### THE CANADIAN MEDICAL ASSOCIATION

## LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

SEPTEMBER 30, 1961 • VOL. 85, NO. 14

#### REVIEW ARTICLE

#### CURRENT STATUS OF **IMMUNIZATION\***

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We are living in the age of active immunization and the use of "multiple" antigens, and there is a high degree of acceptance of this situation by the public and the profession throughout Canada. Prior to the 1939-45 war two antigens were commonly employed, namely diphtheria toxoid and smallpox vaccine, and occasionally typhoid vaccine. Since that time a great array of antigens has been introduced, so many that it became necessary to combine them into what has become known as "combined" or "multiple" antigens, and our present dilemma is that presented by the "multiplicity" of multiple antigens. What are the advantages of combined antigens? A great saving in money, time and effort; a patient may receive as many as six or more antigens in a single injection, thus immeasurably reducing the number of visits. The compounding of antigens into a single mixture does not appear to increase the incidence of reactions or their severity. Further, there is no real "interference" between individual members of a multiple antigen, and it is abundantly clear that the immunity mechanism of the body will respond to many antigens given simultaneously. Actually the bacterial components have been shown to act as adjuvants of the fluid components such as the toxoids and enhance their effectiveness. This has been repeatedly demonstrated both in animals and man. A good example is the D.P.T. mixture1 or the T.A.B.T. mixture wherein the pertussis and the typhoid-paratyphoid fractions enhance the effect of the toxoids.

The following is a list of the multiple antigens currently in common use:

1. For Infants and Young Children (preschool age)

D.P.T.-Polio vaccine, which is made up of pertussis vaccine, poliovirus types I, II and III vaccine and 40 Lf's diphtheria and eight Lf's of tetanus toxoids per c.c.

This is not used for school children or adults, because of the amount of diphtheria toxoid present in the mixture.

2. Booster Doses for School Children

D.T.-Polio vaccine, which is made up of polio-virus types 1, II and III vaccine, 10 Lf's of diphtheria and 10 Lf's of tetanus toxoids per c.c.

This is not for use in adults or for primary immunization, again because of the amount of diphtheria toxoid present.

3. Tetanus-Polio vaccine, which consists of poliovirus types I, II and III vaccine in 10 Lf's of tetanus toxoid and is for use primarily in adults.

4. T.A.B.T. vaccine, consisting of typhoid, paratyphoid A and B bacilli and 8 Lf's of tetanus toxoid per c.c.

5. T.A.B.T.D. vaccine, consisting of T.A.B.T. in 2 Lf's of diphtheria toxoid per c.c. The small amount of diphtheria toxoid, namely 2 Lf's, in this mixture permits its use in adults.

Active immunization of infants and young children is effected by a primary course of three injections of D.P.T.-Polio vaccine one month apart beginning at 3 months of age. Booster doses are recommended at one year, three years and five years of age. This regimen answers the question of when the fourth dose and booster doses of poliomyelitis vaccine should be given to infants and children. The Multiple Antigen Committee of the American Public Health Association recommends that poliomyelitis immunization by injection should not be routinely initiated before 3 months of age<sup>3</sup> because of the limited response in infants owing to the interference by maternal antibodies.

#### Poliomyelitis—Infants

The question has been raised regarding the effectiveness of D.P.T.-Polio vaccine against polio-

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myelitis in young infants who have "maternal antibodies". It has been found that infants with maternal antibodies² do not respond as well to the primary course as infants without maternal antibodies. Nevertheless, when these infants are given a booster dose, most do respond. Thus a more recent recommendation is that infants given D.P.T.-Polio vaccine at three months of age should be given a fourth or booster dose three to six months later. One manufacturer recommends four equal doses at monthly intervals, as the initial series for infants under six months of age.

One group<sup>4</sup> in the U.S.A. has improved the antigenicity of the killed poliovirus vaccine (Salk) by the use of a concentrated, purified and standardized preparation of virus which produces excellent antibody responses after two injections, given at an interval of one month. This product is still in the experimental stage and is not used in the multiple antigens.

#### Adults

It has been customary to give two injections of poliomyelitis vaccine a month apart and a third injection seven months later without any firm recommendation regarding a booster dose. This regimen was adopted as a result of advice from Salk in 1954 when information regarding the most effective dosage schedule was very meagre.

When tetanus-polio vaccine was introduced, the manufacturer recommended three doses a month apart and a booster dose six to twelve months later. This procedure has been generally adopted. Further booster doses at a five-year interval and on receipt of an injury are also recommended.

In the light of the accepted use of this combined vaccine (tetanus-polio), it would seem advisable, when using poliomyelitis vaccine by itself, to administer three injections of 1 c.c. each, one month apart, and to give a booster dose one year later. Further booster doses could be given every two to three years, depending on experience gained by the future use of this vaccine.

#### Live Attenuated Poliovirus Vaccine

Few people realize that the interest in and development of a live poliovirus<sup>5</sup> vaccine preceded the development of Salk vaccine. Many, if not most, virologists felt that solid immunity to poliomyelitis could be produced by the use of a living vaccine only, as in the case of smallpox and yellow fever. For this reason Koprowski, Cox and Sabin developed attenuated strains of poliomyelitis virus for active immunization of man. A vast literature has accumulated on the use of live vaccines from which one may summarize the following:

1. Live vaccines are simple to administer because they may be given by mouth.

2. Infection with live viruses leads to the development of a state of local resistance of the gastrointestinal tract that limits or prevents subse-

quent intestinal multiplication of virus on exposure to infection with a "wild" virus. Salk vaccine apparently does not confer a similar gastrointestinal resistance.

3. Antibody develops quickly in the serum following the gastrointestinal infection.

4. Because of (2) and (3) the use of live virus during an epidemic of poliomyelitis has been suggested to prevent further spread of "wild" virus.

5. The safety of these viruses has been subjected to studies in humans as well as animals, and, generally speaking, the viruses have been found to be innocuous when given to susceptible children and young adults. Until recently, comparatively few susceptible adults of over 20 years have been fed live viruses. Partly for this reason the WHO Expert Committee<sup>6</sup> have recommended accumulation of further data before unlimited use of live vaccine can be recommended in persons of all ages on a community-wide basis. It has been suggested that non-immune adults may develop a more severe infection than do non-immune children. Recent experience in the use of live vaccine does not substantiate this fear, and it is generally agreed that live vaccine may be given to all age groups.

6. The efficacy of live vaccines depends upon multiplication in the gastrointestinal tract. This may be interfered with when all three strains are fed simultaneously. It seems that the highest rates of conversion of individuals from seronegative to seropositive occurs when each type is fed separately. When a trivalent vaccine is fed, in some instances repetition has been necessary to achieve a high conversion rate. Coxsackie, ECHO and "wild" polioviruses act as interfering agents, Sabin, speaking before the American Public Health Association in San Francisco in November 1960, recommended the "blanketing" of the entire population with Type I vaccine, followed within three to four weeks by Type II vaccine, followed within three to four weeks by Type III vaccine. He also recommended the administration of the viruses prior to the poliomyelitis season, preferably in the winter months when the incidence of wild virus infection is at the lowest point. Thus far there has not been a controlled trial with living virus vaccine such as was carried out by Francis with the Salk vaccine, but the evidence to hand on the efficacy of live virus vaccines in humans is favourable. However, much longer periods of observation will be necessary before one can state that the use of live poliovirus vaccines results in any greater reduction in the incidence of poliomyelitis than does Salk vaccine. Salk vaccine has had an excellent record to date. In 1959, in Canada there were 1870 reported cases of paralytic poliomyelitis and 178 deaths. The epidemic occurred mainly among the unvaccinated portion of the population at risk. Seventytwo per cent of cases occurred among the unvaccinated. Kubryk<sup>7</sup> reported the estimated overall effectiveness of three or more doses to be 95.6%, varying with the age group; it was 87.4% effective

in the 0-4 year group, 97.1% effective in the 5-9 year group, and 73.7% effective in the adults 20-39

years of age.

In 1959 there were 193 cases of paralytic poliomyelitis (11.2% of the total) among persons who had received three or more injections and there were 8 fatalities (5.1% of the deaths among this group). It is the latter situation which prompts the desire for a better Salk vaccine or for a live attenu-

The problem which confronts the public and the profession is the extension of complete immunization against poliomyelitis to the entire population, particularly the preschool and adult age groups. There is no age limit in the risk of infection. In 1959 in Canada the youngest patient was seven weeks old and the oldest was 72 years of age, and both died.

The administration of Salk vaccine should be pursued with the greatest vigour prior to the poliomyelitis season. Poliomyelitis can be prevented in the vast majority of instances by the use of Salk vaccine, provided that adequate dosage is given.

#### Tetanus

Active immunization against tetanus should be given top priority, particularly in adults.8,9 The efficacy of tetanus toxoid when given in the proper dosage regimen has been demonstrated beyond any doubt.9 Fortunately, infants and children are being given tetanus toxoid and it was gratifying to find in two groups of young adults, in whom the serum level of tetanus antitoxin was determined, that approximately 50% had sufficient antitoxin as the result of active immunization. This illustrates the progress that is being made in this field, but the adult population needs close attention because, except for those who have served in the armed services or worked in special industrial situations, extremely few adults have had tetanus toxoid. There is no natural immunity to tetanus, and the possibility of contracting the disease exists for all age groups of the entire population. The only method of active immunization against tetanus is by the use of tetanus toxoid.

The other alternative to active immunization is the use of tetanus antitoxin, which is attended with an increasing morbidity rate from serum sickness and in addition fails to prevent or cure the disease in all instances. The use of tetanus toxoid eliminates these problems.

#### Smallpox

The advent of the jet plane, bringing an extremely rapid means of world-wide travel, has made smallpox a global problem. The following intelligence report<sup>10, 11</sup> on epidemic diseases substantiates this remark, "Madrid was officially declared a smallpox infected area February 21, 1961. Fifteen known cases were reported. The disease was imported by a girl aged four, flying from Bombay to Rome to Madrid. The diagnosis was made February 6 and death occurred on February 14." This might happen in Canada, as planes are touching down almost hourly at our international airports from all over the world. Successful smallpox vaccination should be carried out within the first year of life, repeated at least every five years (three years for immigration purposes) and always in the event of an outbreak of the disease. There is no way of determining how many individuals in this province or in Canada are immune to smallpox. In a recent smallpox vaccination program in a primary school in an Ontario city, 25% of the pupils had "primary' takes, and among adults one would expect to find at least 50 to 60% who are not immune to smallpox. There is a clear necessity to increase the numbers of our population who have immunity to smallpox. As an argument against smallpox vaccination, it is said that the procedure produces more serious effects than those resulting from the disease, assuming the almost complete absence of the latter in Canada in the last few years. A vaccinia gamma globulin12, 13 has been prepared which will reduce to a minimum untoward complications following vaccination. This preparation is available in very limited supply through the Canadian Red Cross Society.

#### Measles

The epidemic of measles in Ontario during the past winter (1960-61) is a reminder of the seriousness of this disease, at least from the standpoint of a high morbidity amongst school children, with resulting absenteeism. Fortunately, there is a continuing interest in preparing a suitable protective vaccine, and Enders and his group have been rewarded by their success in the preparation of an attenuated live measles virus vaccine.

The results of the use of this vaccine were reported recently.14 It was shown that in a small group of children previously vaccinated a high degree of protection resulted when the vaccinated children were exposed to clinical cases of the disease. The clinical reaction to the vaccination of 171 susceptible children consisted primarily of fever (83%) and a modified rash (48%); no febrile seizures were noted and Koplik's spots were detected in only 16%. The absence of catarrhal signs was a noteworthy finding. The possibility of febrile seizures is the clinical reaction which might militate against the widespread use of the vaccine as it is developed presently. Further work may lead to the development of an effective live attenuated vaccine which does not produce undesirable side effects.

#### Rabies

The problem of rabies looms with the approach of each summer season. Over the past four or five years the province of Ontario has harboured an epizootic affecting many forms of wild life, particularly the fox and skunk. In the same period doubt about the efficacy of the time-honoured Semple vaccine in preventing rabies in man has led to the preparation of a horse serum which will confer immediate passive immunity to man. This will be followed by active immunity produced by repeated injections of a rabies vaccine. The marked success of the Flury live attenuated rabies vaccine in small animals, particularly the dog, has stimulated interest in the possible use of this type of vaccine in man, but the results of the use of Flury vaccine in man have been disappointing. The risk of neurological complications following the use of a neural vaccine, such as Semple vaccine which is prepared in the rabbit, has led to the introduction of a killed, dried duck-egg embryo vaccine which is virtually free of neural tissue.

In the light of these developments, the Expert Committee on Rabies of WHO15 has made new recommendations concerning the control of this disease. In brief, it is recommended that bites by wild animals and severe multiple face, head, finger, or neck bites by other animals be treated with serum (0.5 c.c. per kg.) which is given immediately and followed by a course of vaccine consisting of a minimum of 14 daily injections. The Committee did not recommend a particular type of vaccine, but pointed out that the incidence of neuroparalytic accidents is high enough in certain areas of the world to indicate the need for further efforts to eliminate these complications. The experience to date shows a decreased incidence of such reactions following the use\* of duck embryo vaccine, but further experience is required before a firm conclusion can be reached concerning the superiority of the avianized vaccine. The serum, though concentrated and purified, is prepared in the horse, and reactions following its administration to humans do occur at about the same frequency as with other sera prepared in this way. The Committee also recommended that in all cases where serum is followed by a full course of vaccine, two supplemental doses of vaccine be administered at 10 and 20 days following the completion of the usual vaccine schedule, and, where possible, these supplemental doses should consist of a vaccine of non-nervous-tissue origin, such as the duck-egg

### Immunization of Man against Rabies before Exposure

This involves individuals exposed to unusual risks, such as veterinarians, dog handlers and laboratory workers, in whom repeated exposure means repeated treatment and increasing risk of severe reactions to the vaccine. The World Health Organization committee recommended that such individuals receive a schedule of immunization consisting of three intradermal doses of avianized vaccine at intervals of five to seven days followed by a booster dose administered one or more months

(preferably two to six months) after the last injection of vaccine. If the individual continues under risk, a similar booster dose should be given every two to three years. Unfortunately, antibody response does not occur in all such vaccinated individuals. This more or less nullifies the value of such a program unless a serum sample is obtained following this course and tested for antibody response. The booster doses should be repeated until an antibody level is detectable. This complicated follow-up procedure detracts considerably from the usefulness of the WHO procedure.

Despite numerous advances in the control of rabies in man, it still remains a difficult problem and with the introduction of horse serum a further hazard is added. In dogs a single injection with the Flury avianized attenuated vaccine apparently con-

hazard is added. In dogs a single injection with the Flury avianized attenuated vaccine apparently confers immunity for at least a year, possibly for three years, and it would be a great advance if a comparable vaccine were available for man. Fenje<sup>16</sup> has reported recently on the successful propagation of rabies virus in tissue culture, which may lead to

an improved vaccine for human use.

#### VIRAL RESPIRATORY INFECTIONS

Influenza

The pandemic of Asian influenza in 1957 was a grim reminder that despite all modern methods for the control of communicable diseases, viral influenza defies them and periodically spreads relentlessly around the world. Influenza is endemic and becomes epidemic periodically: in 1958-59 influenza B virus infection was epidemic in Great Britain and the United States; in 1959-60 Asian virus was epidemic in the Western United States; and during the past winter (1960-61) Asian virus was epidemic in Great Britain, This situation raises the question as to the validity of using a viral influenza vaccine. In the face of a pandemic there is general agreement that a vaccine containing the offending virus should be used. In an emergency, and when the vaccine is in short supply, it could be given to persons in key services such as hospital personnel, telephone operators, firemen and police, but in other situations some experts doubt the value of the use of influenza vaccine. Evaluations of influenza vaccine have demonstrated that two doses may be from 60 to 75% effective in preventing influenza. The Commission on Influenza of the Armed Forces Epidemiological Board, with extensive experience in the use of influenza vaccine, has recommended the use of a polyvalent viral vaccine containing representatives of the three types of A virus and the B group during the period between pandemics. In the past four years there has been a higher mortality among the aged and those with chronic cardiovascular, pulmonary, renal or metabolic diseases, and among pregnant women. It would seem justifiable to use influenza vaccine for these groups in the face of an epidemic. Industry is interested in this problem, and there seems justification for the use of a polyvalent viral vaccine given in advance of the winter season. The immunity is short-lived and possibly persists for a year only. It should be appreciated that the clinical entity commonly known as the "flu" or, a "cold" may be caused by a great variety of viruses<sup>17</sup> and that the use of a viral influenza vaccine results in an immunity that is very specific.

#### Adenovirus Group

These agents have been shown to be the cause of outbreaks of acute respiratory infections clinically indistinguishable from "flu", chiefly among young recruits to the armed forces. 17 A vaccine has been produced which has been shown to be quite effective in protecting against viruses of this group, but, thus far, the incidence of these infections in the civilian population is almost negligible. For this reason, the use of adenovirus vaccine in the civilian population does not seem justified for the present.

#### Infectious Hepatitis (Jaundice)

This disease is apparently on the increase in North America, which is surprising because it is believed to be spread by way of the gastrointestinal tract but possibly by inhalation as well. With our advanced knowledge of handling foods and high standard of living, one would have expected a marked reduction in the incidence of a disease spread by the fecal-oral route, but the increase may be due to the fact that foods are prepared on a vast scale and distributed over a wide area. In any event, as in many other communicable diseases, the most effective method of control probably will be through the use of an effective immunizing agent. Thus far the isolation and identification of the etiological agent has evaded a determined search by a group of courageous workers. At the recent Atlantic City meeting of the Federation of Societies for Clinical Research, a report from workers at the National Institutes of Health<sup>18</sup> described a cytopathogenic agent isolated from an icterogenic human serum which had been propagated in tissue culture. This may be the causative agent of serum hepatitis, and the discovery of it may lead to the development of a vaccine for active immunization against infectious hepatitis. Currently, the only agent available for the prevention of infectious hepatitis is gamma globulin and reports in the literature recommend varying amounts of gamma globulin for use in human immunization from 0.01 c.c. per lb. to as much as 0.08 c.c. It is the consensus that 0.02 c.c. per lb. of body weight is the optimal amount and it should be administered to the contacts within ten days and not later than two weeks after the appearance of jaundice in the index case. In the case of pregnancy larger doses are recommended, as much as 0.14 c.c. per lb. of body weight.

#### SUMMARY

A series of multiple antigens is available for the active immunization of infants and children and adults against diphtheria, tetanus, whooping cough and Polioviruses types I, II and III.

Young infants with maternal antibodies require more antigen than those without such antibodies.

Salk vaccine has been shown to be a very effective agent when given in suitable dosage. The entire population should be actively immunized.

Live attenuated poliovirus vaccine may merit an important place in the control of paralytic poliomyelitis.

Tetanus toxoid should be used in all age groups to control a serious disease and to eliminate the troublesome practice of passive immunization with antitoxin.

The control of smallpox has become a global problem; the population should be kept actively immunized.

The control of measles by the use of a live attenuated vaccine may be practicable in the near future.

A recent development in the prevention of rabies in man is the introduction of a serum for early passive immunization which is followed by daily injections of vaccine. A non-neural vaccine is coming into use.

Acute respiratory virus infections have an important role in producing an increasing amount of morbidity and mortality. Viral influenza vaccine has been shown to be useful in certain situations.

The isolation and identification of the etiological agent of infectious hepatitis has not been achieved despite intensive investigation. Gamma globulin is still the recommended agent for passive protection.

#### · REFERENCES

- GREENBERG, L. AND FLEMING, D. S.: Canad. J. Pub. Health, 38: 279, 1947; also 39: 131, 1948.
   MACLEOD, D. R. E.: Status of combined vaccine, In: The 5th International Poliomyelitis Conference of the International Poliomyelitis Congress, Copenhagen, July 26-28, 1960, p. 15.

- International Poliomyelitis Congress, Copenhagen, July 26-28, 1960, p. 15.

  3. American Public Health Association, Committee on Multiple Antigens: Am. J. Pub. Health, 51: 604, 1961.

  4. HILLEMAN, M. R. et al.: Acad. Med. New Jersey Bull., 6: 106, 1960.

  5. RHODES, A. J.: Canad. J. Pub. Health, 52: 45, 1961.

  6. World Health Organization, Expert Committee on Poliomyelitis, Third report, World Health Organization Technical Report Series No. 203, 1960.

  7. KUBRYK, D.: Canad. J. Pub. Health, 51: 389, 1960.

  8. SHERMAN, C. D., JR. AND BARNHOUSE, D. H.: J. Occup. Med., 3: 75, 1961.

  9. EDSALL, G.: J. A. M. A., 171: 417, 1959.

  10. Canada, Department of National Health and Welfare, Epidemiology Division: Surveillance report of epidemic or unusual communicable diseases, 5: Mar. 11, 1961.
- demic or unusual communicable diseases, 5: Mar. 11, 1961.

  11. Idem: Ibid., 5: April 8, 1961.

  12. KEMPE, C. H.: Pediatrics, 26: 176, 1960.

  13. News and Announcements: Ibid., 26: 336, 1960.

  14. KATZ, S. L. et al.: New England J. Med., 263: 180, 1960.

  15. World Health Organization, Expert Committee on Rabies, Fourth Report, World Health Organization, Technical Report Series No. 201, 1960.

  16. FENJE, P.: Canad. J. Microbiol., 6: 479, 1960.

  17. World Health Organization, Expert Committee on Respiratory Virus Diseases, First report, World Health Organization, Technical Report Series No. 170, 1959.

  18. O'MALLEY, J. P. AND MEYER, H. M., JR.: Fed. Proc., 20: 446, 1961 (abstract).

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#### ORIGINAL ARTICLES

# AN EXPERIMENTAL MODEL OF "DERMATOMYOSITIS" INDUCED BY CALCIPHYLAXIS\*

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EXPERIMENTAL MODELS of disease can offer considerable help in the elucidation of pathogenetic problems and in the search for therapeutic measures that might be applicable to the corresponding spontaneous maladies of man. Of course, a reproduction or dummy is never equivalent to the original: the metabolic derangement induced by pancreatectomy in the dog is far from duplicating clinical diabetes mellitus; the transplantable tumours of mice are not identical with the spontaneous neoplasms of man, and a culture of microbes in vitro is even less comparable to the infectious disease that the same germs produce in higher organisms. Yet, all of these and many other "working models" of morbid processes proved to be useful tools in the study of spontaneous diseases.

Since 1932, our group has been engaged in perfecting six experimental models of so-called mesenchymal or collagen diseases in the most commonly used experimental animal, the rat. These were: (1) the "hyalinosis" with malignant nephrosclerosis, periarteritis nodosa, myocarditis and hypertension that can be induced by desoxycorticosterone overdosage18 or by the "endocrine kidney" operation; 19 (2) the topical "irritation arthritis" elicited by the injection of formalin or other irritants into the paw;<sup>20</sup> (3) the "granuloma pouch" technique for the study of inflammation;21 (4) the necrotizing or calcifying cardiopathies that result from combined treatment with various electrolytes and steroids;24,27 (5) the "anaphylactoid inflammation" that ensues after a single injection of certain challengers, such as egg white or histamine liberators;17, 22 and (6) the calcifying scleroderma-like lesions elicited under certain conditions by overdosage with parathyroid hormone<sup>15, 16</sup> or dihydrotachysterol.<sup>23</sup> None of these experimental models are exact replicas of the clinical conditions they attempt to imitate, yet they helped to call attention to the role of corticoids in the pathogenesis of mesenchymal diseases, thereby suggesting novel therapeutic applications of glucocorticoids and antimineralocorticoids. They also furnished us with test objects for the quantitative assay of prophlogistic and antiphlogistic compounds that are of clinical interest. These were the considerations that encouraged our attempts to devise some kind of mesenchymal syndrome that would resemble dermatomyositis, a disease for which no experimental model is available as yet.

In the course of our studies on calciphylaxis, we noted that in rats sensitized with the vitamin-D derivative, dihydrotachysterol (DHT), subsequent challenge by ferric dextran (Fe-Dex) plus certain histamine liberators (e.g. polymyxin) causes a peculiar, acute, usually fatal form of musculocutaneous inflammation, which reminded us of dermatomyositis.

Calciphylaxis is a condition of hypersensitivity in which, during a "critical period" after sensitization by a systemic calcifying factor (e.g. vitamin-D compounds, parathyroid hormone, sodium sulfathiazol), treatment with certain challengers (e.g. metallic salts, Fe-Dex, egg white) causes an acute, local calcification followed by inflammation and sclerosis. A topical calciphylaxis thus induced by subcutaneous injection of challengers results in a cutaneous calcinosis reminiscent of calcareous scleroderma. However, in suitably sensitized (e.g. DHT-treated) rats, calciphylactic reactions can also be elicited rather selectively at predetermined sites (e.g. in the pancreas, bile ducts, uterus, spleen, Kupffer cells, lungs, salivary glands, lacrimal glands or the carotid body) by the intravenous administration of challengers that have a particular affinity for one or the other organ.25, 26, 29, 31

In many instances, the sensitivity of animals to both local and systemic challengers can be enormously enhanced if, in addition to DHT given orally, they also receive small doses of iron intravenously. For example, histamine produces no local calciphylactic response in rats sensitized only by DHT but does elicit pronounced topical calcification and inflammation if the animals are pretreated with Fe-Dex in addition to DHT. It is the object of this report to describe a simple technique for the production of a systemic acute musculocutaneous inflammation that can be elicited by certain histamine liberators, following such combined sensitization with DHT plus Fe-Dex. We shall also attempt to analyze the pathogenesis of this experimental disease, without attempting to decide, however, whether it is closely related to the dermatomyositis of man,

#### MATERIALS AND TECHNIQUES

Many preliminary experiments had to be performed to establish the optimum conditions (dosage, route of administration, spacing of treatments ["critical period"], selection of most appropriate iron preparations and histamine liberators) for the production of the musculocutaneous syndrome; however, for the sake of brevity, we shall merely mention a few of these initial observations later in the discussion. Here we shall limit ourselves to a

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TABLE I.—Experimental Dermatomyositis Induced by Calciphylaxis

Group	Treatment	Observations	Mortality %
1	DHT	Occasional traces of calcification in kidney, heart, gastric mucosa.	0
2	Fe-Dex	Moderate iron deposition in tissues, especially in the R-E system.	0
3	PMX	Transient anaphylactoid inflammation of skin, particularly in acral regions, lasting few hours only. Mastocyte degranulation.	0
4	DHT+Fe-Dex	Mere summation of changes seen in Groups 1 and 2.	0
5	DHT+PMX	Summation of changes seen in Groups 1 and 3 plus more chronic erythroderma and moderate mast cell granule calcification.	0
6	Fe-Dex+PMX	Mere summation of changes seen in Groups 2 and 3.	0
7	DHT+Fe-Dex+PMX	<ul> <li>2nd-3rd day: erythema, edema and pain in skin of face, ears and frontal extremities; stomatitis. Postmortem: hyperemia, whitish discolouration and edema of muscles, especially underneath affected skin regions; hyperemia and edema of brain.</li> <li>3rd-6th day: induration with nonpitting edema of skin, scales, great muscular weakness. Postmortem: diffuse mucoid edema and moderate calcification of skin, fasciae, muscles, periarticular regions and occasionally myocardium. Affected muscles greyish, have doughy consistency. Mast cells degranulated, swollen, vacuolated, their granules scattered throughout connective tissue and many of them calcified. Moderate osteoporosis.</li> </ul>	

detailed description of one experiment with the most consistently successful technique.

Seventy female Holtzman rats with a mean initial body weight of 95 g. (range 92-100 g.) were subdivided into seven equal groups and treated as indicated in Table I.

DHT (dihydrotachysterol, Calcamin,® Dr. A. Wander S.A., Basel, Switzerland) was administered at the dose of 1 mg, in 0.5 ml. corn oil by stomach tube once on the first day to Groups 1, 4, 5 and 7. Fe-Dex (ferric dextran, Imposil,® Benger Laboratories, London, England) is a preparation which contains 75 mg, of metallic iron per ml, as ferric hydroxide in complex with a low molecular weight dextran fraction. This product was diluted with distilled water to 1/75 of the original strength and 1 ml, of the resulting solution (equivalent to 1 mg. of iron) was given intravenously on the second day to Groups 2, 4, 6 and 7. PMX (Polymyxin B Sulfate B.P., Burroughs Wellcome and Co., Canada, Ltd.) is an antibiotic which also acts as a histamine discharger and mast-cell depleter. It was administered at the dose of 2 mg, in 0.2 ml. water, subcutaneously, once on the second day to Groups 3, 5, 6 and 7.

The animals were kept exclusively on "Purina Fox Chow" (Purina Co. of Canada) and tap water. On the sixth day, the experiment was terminated by killing all survivors with chloroform. At autopsy the organs were inspected with a stereoscopic loupe and specimens of the skin, skeletal muscle, heart and kidney were fixed in alcohol-formol (8 parts absolute alcohol, 2 parts 10% formalin) for the subsequent staining of paraffin-embedded material with the von Kossa and celestine-blue methods<sup>26</sup> for calcium and with cresyl violet, methylene blue or toluidine blue for mast cells. The development of skeletal lesions was followed on specimens of various bones, fixed and simultaneously decalcified

in Susa solution, saturated with picric acid. Following embedding in paraffin, sections of these specimens were stained with hematoxylin-phloxine or the PAS-method.

#### RESULTS

Table I summarizes the principal results of this experiment,

The single oral dose of *DHT* given here (Group 1) produced no obvious change in the behaviour of the rats; even postmortem examination revealed only traces of calcification in the kidney, heart or gastric mucosa of occasional animals. These are normally the most sensitive organs in which massive calcification can be produced regularly by much larger doses of *DHT*, especially in the case of chronic treatment.

The single, comparatively small dose of Fe-Dex (Group 2) failed to elicit any manifest clinical disturbances and postmortem study revealed only traces of iron, especially in the reticuloendothelial system.

In agreement with earlier observations, *PMX* (Group 3) caused a typical though quite evanescent anaphylactoid inflammation. This manifested itself by a hyperemia and moderate swelling of the paws, snout, ears and, to a lesser extent, of the entire skin surface. The reaction lasted only a few hours after the injection and was histologically characterized by serous inflammation with mast cell degranulation,

Treatment with *DHT plus Fe-Dex* (Group 4), *DHT plus PMX* (Group 5) or *Fe-Dex plus PMX* (Group 6) resulted essentially in a summation of the changes normally obtained by these agents when given alone. Only three of the rats in Group 5 showed a more pronounced cutaneous reaction than could be obtained by PMX alone; here, histologic examination revealed mild degrees of the

musculocutaneous changes that were fully developed in all animals of Group 7.

In sharp contrast to the rats of the first six groups, all the rats treated with DHT, Fe-Dex plus PMX (Group 7) became seriously ill immediately after treatment with PMX and four of them died between the third and fifth day of the experiment, Clinically, the most striking features of the resulting syndrome were a pronounced, painful symmetrical erythema and nonpitting edema of the skin covering the face (particularly the periorbital region), ears and frontal extremities. Judging by the few animals that died during the first days of the experiment, the hyperemia and edema also affected the muscles in the same region as well as the brain. Beginning on the third day and progressing to the end of the experiment, there developed a patchy stomatitis while the affected skin regions became indurated and scaly, although the erythroderma tended to disappear. Finally, severe muscular weakness set in,

At autopsy, the most striking change was a diffuse nonpitting edema and moderate calcific infiltration of the skin, the subcutaneous tissue, fasciae and muscles, again particularly around the face, ears, neck and frontal extremities. In the affected regions, the muscles assumed a light greyish colour and a peculiar doughy consistency. At the same time, there developed a moderate degree of cortical nephrocalcinosis and, occasionally, inflammation with calcification could be detected in the myocardium.

The most striking histologic changes in the skin were patchy liquefaction necrosis of the epidermal junction, mucoid degeneration of connective tissue and subcutapeous fat with diffuse clusters of fine calcium granules. Occasionally the surface epithelium became detached in the form of scales. The blood vessels were engorged, especially in the nuchal region, but perivascular infiltrations were rare. In the musculature, degenerative and inflammatory changes varied greatly in intensity but usually the changes were most severe in the regions covered by the most seriously affected skin. The cross-striation tended to disappear, the sarcoplasm became swollen, homogeneous and often fragmented; in certain patches it disappeared completely, while the nuclei exhibited intense proliferation. Here also, the interstitial tissue contained numerous minute clusters of calcium granules. Essentially, similar changes were observed around the joints in association with panniculitis and mild periarticular calcification, especially in the elbow joint, knee joint and shoulder joint. In some places, fat and muscle were completely replaced by inflamed fibrous tissue. The myocardium was more irregularly affected, but the lesions, where present, histologically resembled those seen in skeletal muscles. The bones uniformly exhibited a moderate degree of osteoporosis (Fig. 1).

A less conspicuous but, to our mind, particularly important histologic change, which was quite constant in all affected regions, concerned the mastocytes. In the rat, the skin normally contains very many compact mastocytes, which are so filled with granules that the nucleus is rarely visible. In the affected regions, such normal mastocytes could never be found, even around the lips and the base of the ears, which usually contain the greatest accumulations of these cells. Instead, small clusters of minute calcified granules were seen distributed approximately in the number and location normally characteristic of mastocytes. On sections simultaneously stained with the von Kossa technique (for calcium) and with cresvl violet, toluidine blue or methylene blue (for mast cells), these clusters almost invariably contained both regular small granules that stained metachromatically with mast-cell dyes and irregularly shaped larger granules tingeable with von Kossa's stain. In many instances, the nucleus and the swollen, vacuolated cytoplasm of a mast cell could clearly be distinguished in the midst of these clusters (Fig. 2).

#### Discussion

It is evident that following sensitization with a single oral dose of DHT, calciphylactic challenging by combined treatment with Fe-Dex plus PMX has produced a systemic musculocutaneous inflammation, accompanied by calcification and frequently conducive to death. Whether this syndrome is closely related to dermatomyositis as it occurs in man must, meanwhile, remain undecided. It would be futile to belabour this point, especially since nothing is known either about the etiology or about the manifestations of dermatomyositis that could serve as a decisive pathognomonic criterion.

We can say only that both the calciphylactic syndrome just described and clinical dermatomyositis are characterized by an essentially similar distribution and histologic structure of the lesions: a particular predilection for skin and muscles, especially those of the face and extremities, with progression from hyperemia and edema towards inflammation, sclerosis and sometimes gross calcification. All these features of the experimental syndrome have repeatedly been recognized as characteristic of clinical dermatomyositis.<sup>9, 11, 32-34</sup>

Fig. 1.—General appearance of the musculocutaneous lesions. A. Left: DHT+PMX treated rat shows just detectable lesions in skin of head and neck. Right: treatment with DHT+PMX+Fe-Dex induces pronounced inflammation and calcification of the skin, particularly that covering cranial half of body. B. Same two rats with skin split along midline of dorsum and reflected to sides. Here lesions in subcutia and musculature are especially obvious. C. Left front paws of another pair of similarly treated rats. Only animal given DHT+PMX+Fe-Dex (right) shows lesions in and around muscles. D. Histologic appearance of severely affected skin after DHT+PMX+Fe-Dex. Scaling with inflammation and calcification of derma. Liquefaction necrosis along epithelial attachment and (left upper corner) within epithelium itself. E. Edema, hyalinization and fragmentation of more advanced stage. Dark spots correspond to calcium deposits (v. Kossa, × 120).

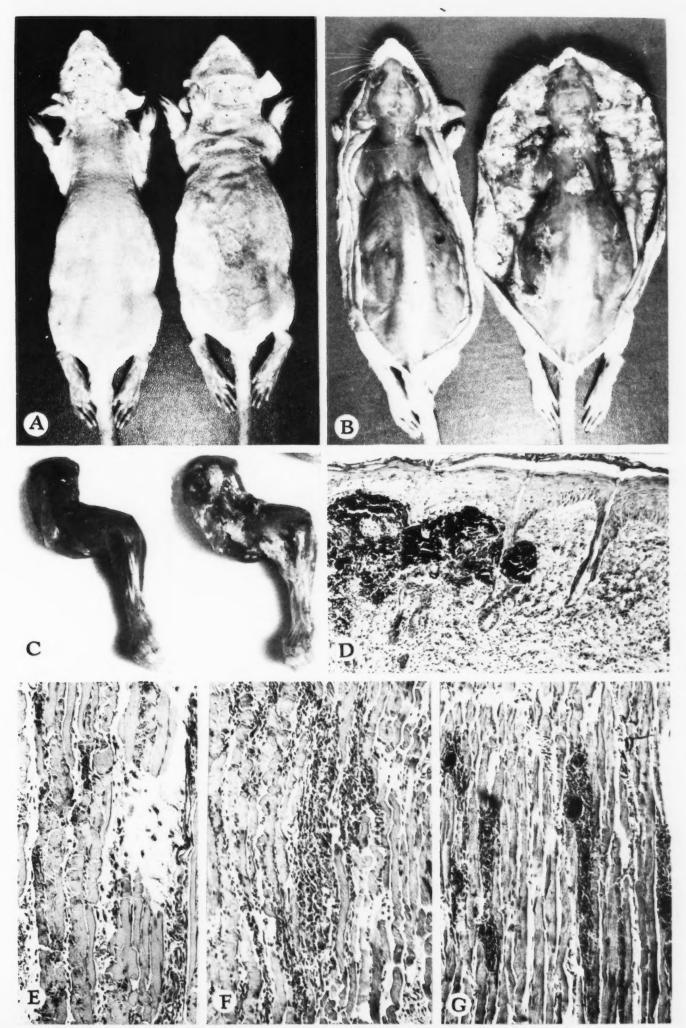


Fig. 1.—General appearance of the musculocutaneous lesions.

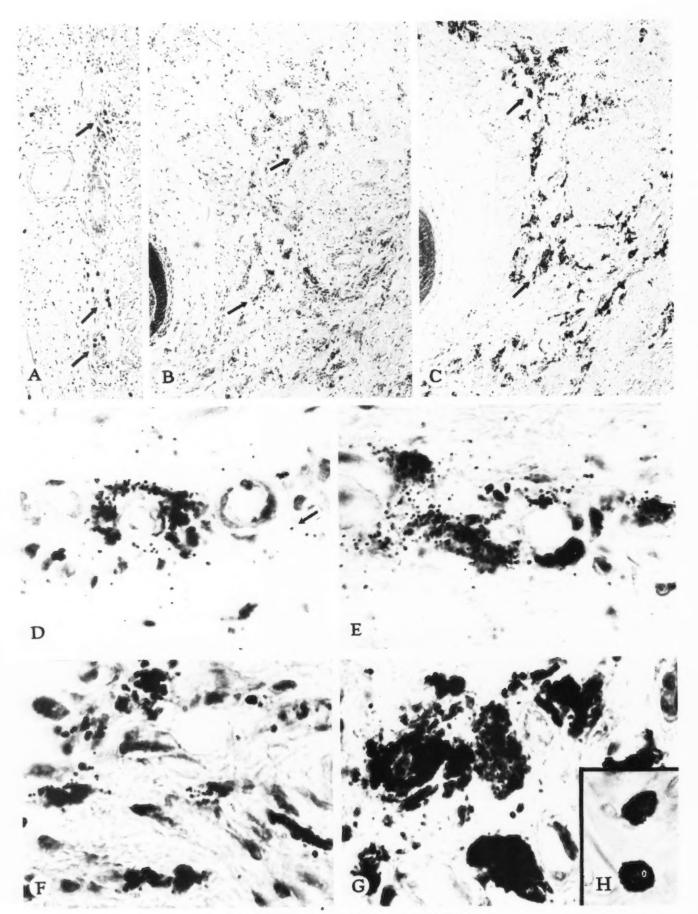


Fig. 2.—Mast-cell "explosion" and calcification.

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A close relationship between all the collagen diseases and soft-tissue calcification has long been suspected on clinical grounds.<sup>36</sup> An osteoporosis similar to that seen in our rats is likewise common in clinical dermatomyositis,<sup>2</sup> although in our experimental syndrome, the rapidity and intensity of the calcium deposition was sometimes almost reminiscent of the clinical entity of "acute soft-tissue calcinosis".<sup>7</sup>

The high incidence of spontaneous neoplasms in patients with dermatomyositis is puzzling but sufficiently well established to be mentioned in most of the textbook descriptions of the disease. 13, 14 Our short-term experiments naturally offered no opportunity to explore this particular point, but many of our calciphylactic rats exhibited patches of squamous metaplasia in the tracheal epithelium. It may also be relevant to mention that the carcinogenic properties of Fe-Dex have been so clearly demonstrated that the preparation had to be withdrawn from clinical use.1 In this connection, it is perhaps also significant that a rather similar musculocutaneous calciphylactic syndrome is obtained in DHT-sensitized rats challenged by Thorotrast,® another carcinogenic preparation.30

Innumerable observations in man revealed a close association between calcium and iron deposition.<sup>3-5, 8, 10</sup> Furthermore, both Ehrlich,<sup>6</sup> the discoverer of the mast cell, and Westphal,<sup>35</sup> his pupil, were impressed with the abundance of mast cells in hemosiderosis of the lung. In addition, several clinicians and experimenters demonstrated close and apparently causal relationships between mast-cell activity on the one hand and inflammation, sclerosis or even keloid formation, on the other, mast-cell proliferation being particularly prominent in inflammation induced by tumours or carcinogens.<sup>12</sup>

These points are mentioned only to call attention to the possible existence of correlations between metal (particularly calcium and iron) metabolism, collagen disease and carcinogenesis as a fruitful field for further research. But, of course, none of the studies quoted offer any support to the view that the musculocutaneous inflammation and calcification that we produced with the aid of an iron preparation is essentially related to dermatomyositis.

Much more specific information is available as regards the pathogenesis of our experimental syndrome itself, considered quite apart from any possible clinical implication. It is clear that none of the three ingredient pathogenic factors-DHT, Fe-Dex and PMX-alone can produce this syndrome; indeed, even combinations of any two among these agents are ineffective, with the possible exception of DHT plus PMX. In a few rats, the latter combination did cause slight musculocutaneous lesions, though even these might have depended on endogenous iron, since very minute amounts of this metal can act as calciphylactic challengers. In any event, the regular production of a marked calciphylactic syndrome of this type depends upon sensitization by a calcifying agent (DHT), an iron compound (Fe-Dex) and a histamine discharger (PMX).

In the course of the preliminary experiments (briefly mentioned in our introduction), we showed that Fe-Dex can be replaced by ferric chloride (1 mg. or more, subcutaneously) and polymyxin by the histamine discharger 48/80 (2 mg., subcutaneously) under otherwise identical experimental conditions. Histamine itself (20 mg. twice, subcutaneously) cannot replace PMX in this respect. However, histamine causes massive local calcification at the site of injection when given concurrently with intravenous Fe-Dex to the DHT-sensitized rat, while in animals sensitized only with DHT, the same dose of histamine produces no local calcium deposition. All these observations are compatible with the view that, after sensitization with a systemic calcifying agent such as DHT in the presence of iron (supplied in various forms), diverse histamine dischargers can elicit our experimental simile of dermatomyositis. It is known that histamine dischargers also discharge the granules of mast cells and that the latter are rich in histamine.12 It is conceivable, therefore, that under our experimental conditions, inflammation is induced by the local irritating effect of minute calcium granules formed around the discharged mast-cell granules because these contain histamine. If this were so, many types of inflammation and sclerosis could be essentially due to the transient deposition of calcium in connective tissue. Such a process could readily escape the attention of pathologists unless the tissues were examined on specially fixed and stained preparations during the (presumably brief) period before the small granules are absorbed.

Of course, the mastocyte granules contain many substances apart from histamine, but the concept of their participation in calcinosis and sclerosis does not depend upon the assumption that histamine itself plays a decisive role. There is much evidence in support of the view that mast cells also produce serotonin, heparin and various mucopolysaccharides. Under our experimental conditions, serotonin (0.05, 0.5 or 5 mg., subcutaneously) and heparin (2, 20 or 200 I.U., subcutaneously) in-

Fig. 2.—Mast-cell "explosion" and calcification. A. Compact mast cells (on slide purple, here black) in normal subcutaneous tissue. Main accumulations marked by arrows. No trace of calcification (v. Kossa + methylene blue, × 120). B. Distribution of "exploded" mast cells in subcutaneous tissue near bristle hair of lip after treatment with DHT+PMX+Fe-Dex. The granules (on slide purple, here grey) have been discharged into surroundings (methylene blue, × 120). C. Adjacent section stained both for mast-cell granules (methylene blue) and for calcium (v. Kossa). Each cluster corresponds to mixture of uncalcified (here grey) and calcified (black both on slide and here) mast-cell granules (A, B and C, × 120). D, E, F and G. Successive stages in the calcification of discharged mast-cell granules. Uncalcified granules are purple, small and regular (one marked by arrow in D) while upon calcification they become larger and coalesce into black clumps (v. Kossa + methylene blue, × 1000). H. Two normal mast cells for comparison (staining and magnification as in D-G).

duced no dermatomyositis-like lesions and only occasional topical calcification in the DHT plus Fe-Dex-treated rat; in animals sensitized only with DHT the compounds did not even elicit calcification at the site of injection. On the other hand, chondroitin sulphuric acid (2 mg., subcutaneously) produced marked local calcification in rats sensitized with DHT alone. The lesions were even more pronounced after treatment with DHT plus Fe-Dex, but dermatomyositis-like systemic lesions did not ensue. The production of the generalized musculocutaneous changes may therefore depend upon the simultaneous effect of several of these mast-cell constituents, upon their more protracted action (such as would ensue during gradual liberation from the cells) or upon other hitherto not tested mast-cell components.

Much further work will be necessary to identify the particular mast-cell constituent(s) that acts as a matrix or mordant for calcium deposition, However, our findings do appear to show conclusively that, after being discharged from the cell, the mastocyte granule can attract and precipitate calcium in a form suitable for the diffuse infiltration of the connective tissue by this notoriously irritating and sclerosis-producing metal,

Finally, the present investigations also raise the question of the possible relationship between the experimental connective tissue diseases produced by calciphylaxis and those elicited by hormones (e.g. mineralocorticoids, anterior pituitary extracts). The fact that calciphylaxis can be prevented by hypophysectomy28 suggests that the two types of morbid lesions may be interdependent, although sodium is the principal conditioning factor for the induction of hyalinosis by hormones while calcium occupies the central role in the induction of calciphylaxis.

#### SUMMARY

Diffuse inflammation with connective tissue proliferation and calcification of musculocutaneous structures can be produced by calciphylaxis in the rat. This morbid change may serve as an experimental model of dermatomyositis since it resembles this disease in many respects without necessarily being causally related to it.

The calciphylactic treatment, necessary for the production of this disease model, consists of sensitization with dihydrotachysterol (DHT) followed by challenge with ferric dextran (Fe-Dex) and a histamine discharger such as polymyxin (PMX).

The pathogenic process apparently responsible for this experimental syndrome is the explosive discharge of mast-cell granules, which subsequently undergo calcification. The resulting calcified granules stimulate inflammation and connective tissue proliferation, particularly in those areas of the muscular and cutaneous systems where mast cells are notoriously abundant.

The possible relationship of this form of calciphylaxis to the other inflammatory and collagen diseases is also briefly discussed.

This work was supported by the National Institutes of Health, U.S. Public Health Service (Grants Nos. A-1641, B-2037, H-3688 and H-6182), the Medical Research Council of Canada (Consol. Grant No. 11) and The Office of the Surgeon General, U.S. Army Medical and Research Company of Contract No. 12, MD 2020 mand, Contract No. DA-49-193-MD-2039.

#### REFERENCES

- Medical News: Brit. M. J., 1: 890, 1960.
   BABEAU, P. AND PASCAL, J. P.: Algérie méd., 64: 1081,

- BABEAU, P. AND PASCAL, S. P.: Algerie mea., 64: 1081, 1960.
   BUNTING, H.: A.M.A. Arch. Path., 52: 458, 1951.
   CAMERON, G. R.: J. Path. & Bact., 33: 929, 1930.
   DAHL, L. K.: J. Exper. Med., 97: 681, 1953.
   EHRLICH, P.: Arch. Anat. Physiol., 3: 166, 1879.
   FEUER, S. G. AND FLIEGEL, O.: Arch. Phys. Med., 42: 492, 1961.
   GIERKE, E.: Arch. path. Anat., 167: 318, 1902.
   KEIL, H.: Arch. Int. Med., 66: 339, 1940.
   LUBARSCH, O. AND PLENGE, K.: Die Krankhaften Ablagerungen und Speicherungen. In: Handbuch der speziellen pathologischen Anatomie und Histologie (F. Henke and O. Lubarsch. editors), Springer Verlag, Berlin, Vol. 3, Part 3, 1931, p. 607.
   O'LEARY, P. A. AND WAISMAN, M.: Arch. Dermat. & Syph., 41: 1001, 1940.
   RILEY, J. F.: The mast cells, E. & S. Livingstone, Ltd., Edinburgh, 1959.

- Vol. 3, Part 3, 1931, p. 607.
  O'LEARY, P. A. AND WAISMAN, M.: Arch. Dermat. & Syph., 41: 1001, 1940.
  RILEY, J. F.: The mast cells, E. & S. Livingstone, Ltd., Edinburgh, 1959.
  ROBBINS, S. L.: Textbook of pathology, with clinical applications, W. B. Saunders Company, Philadelphia, 1957.
  SAPHIR, O., editor: A text on systemic pathology, Vol. I, Grune & Stratton, Inc., New York, 1958.
  SELYE, H.: J. A. M. A., 99: 108, 1932.
  Idem: Virchows Arch. path. Anat., 286: 91, 1932.
  Idem: Endocrinology, 21: 169, 1937.
  SELYE, H. AND PENTZ, E. I.: Canad. M. A. J., 49: 264, 1943.
  SELYE, H. AND PENTZ, E. I.: Canad. M. A. J., 49: 264, 1943.
  SELYE, H. AND STONE, H.: J. Urol., 56: 399, 1946.
  SELYE, H.: Brit. M. J., 2: 1129, 1949.
  Idem: J. Allergy, 25: 97, 1954.
  Idem: J. Invest. Dermat., 29: 9, 1957.
  Idem: J. Invest. Dermat., 29: 9, 1957.
  Idem: The chemical prevention of cardiac necroses, The Ronald Press Co., New York, 1958.
  SELYE, H., JEAN, P. AND VEILLEUX, R.: Proc. Soc. Exper. Biol. & Med., 104: 409, 1960.
  SELYE, H. AND NIELSEN, K.: Acta morphol. Acad. Sci. Hung., 10: 327, 1961.
  SELYE, H.: The pluricausal cardiopathies, Charles C Thomas, Springfield, Ill., 1961. (To be published.)
  SELYE, H.: Allergie & Asthma. In press, 1961.
  SELYE, H.: GENTILE, G. AND VEILLEUX, R.: Brit. M. J. In press, 1961.
  SELYE, H.: Biochim. e biol. sper. In press, 1961.
  SELYE, H.: Biochim. e biol. sper. In press, 1961.
  TALBOTT, J. H. et al.: Arch. Int. Med., 63: 476, 1939.
  TALBOTT, J. H. et al.: Arch. Int. Med., 66: 476, 1939.
  TALBOTT, J. H. et al.: Arch. Int. Med., 66: 476, 1939.
  TALBOTT, J. H. et al.: Franchische Untersuchungen, Hirschwald, Berlin, 1891, p. 17.
  Wheeler, C. E. et al.: Ann. Int. Med., 36: 1050, 1952.

#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

The profession of medicine seeks nothing for itself. It has no secrets. All it knows and all it can do is for the healing of the people. It has no existence apart from the public good, and the whole history of medicine teaches that the people are best served when the profession is at the high level whereat its founder placed it. The Chinese entertain a contrary opinion. To them a physician is a kind of scavenger and nothing more. He is paid by the piece, and his pay stops when his work is done badly; but it is not a fact that China is more free from disease than England is, or that its inhabitants are more comfortable and safe in sickness.

The relation between physician and patient is not an affair of contract. It is based upon necessity on the one hand, and willingness to serve on the other. The patient is free to ask: the physician is free to serve; and the reward is an afterthought, an affair for future consideration. This is the system which humanity has evolved for itself, and where it is most completely employed humanity is best served.-Excerpt from editorial, Canad. M. A. J., 1: 886, 1911.

# SIGNIFICANT BACTERIURIA IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN\*

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THE EXACT explanation of the greater frequency of positive urine cultures in females is one of the most vexing problems in medicine today. Chronic pyelonephritis is being recognized increasingly as a cause of significant morbidity and mortality in the long-term follow-up of patients with asymptomatic bacteriuria. Kass<sup>1</sup> and Kass, Miall and Stuart<sup>7</sup> showed that asymptomatic bacteriuria can be detected in at least 6% of females and 4% of males in an outpatient department, and is correlated with hypertension in a significant way. Asymptomatic bacteriuria in the general population is of sufficient magnitude and importance to warrant investigation of its cause because bacteriuria may be the starting point for acute pyelonephritis, and the focus which leads to recurrent or chronic pyelonephritis.

In the female, direct lymphatic communications between cervix, vagina and bladder have been demonstrated,2,3 and the frequent association of infection of the cervix and vagina with trigonitis is a relatively common observation which probably explains part of the overall difference in the incidence of bacteriuria between males and females. The author has made the untested observation that urinary complaints are more frequent in postmenopausal patients, but the relationship between a lowered menopausal level of estrogen and the presence of bacteriuria has never been studied. The present communication describes an investigation of this possibility, in which an attempt to determine whether there was any relationship between symptoms, endocrine status, pelvic findings, and colony counts of the urine of premenopausal and postmenopausal females was carried out because it seemed important to determine whether a low estrogen level is a significant factor in determining susceptibility to urinary tract infections.

#### MATERIALS AND METHODS

The majority of the patients in this study were seen at the gynecological clinic of the Jewish General Hospital, Montreal, but a few inpatients were also included to make up the 100 premenopausal and 100 postmenopausal patients. These patients were chosen by the nursing staff in a random fashion.

The vulva and urethral orifice of each patient were cleansed with sponges soaked with aqueous benzalkonium chloride (Zephiran), and a sterile catheter was inserted into the bladder. Urine specimens were sent immediately to the laboratory

or were stored in the refrigerator at a temperature of less than 4° C. Kass<sup>6</sup> has noted that such storage does not significantly alter colony counts.

The laboratory procedures were as follows:

1. A sample of urine was cultured on blood agar plates, McConkey's agar plates and in Bacto-peptone broth and incubated for 18 hours at 37° C.

2. If a specimen showed growth: (a) Identification of organisms was established by standard morphological and biochemical tests. (b) Two dilutions, 1/100 and 1/1000, were prepared of the original urine sample which had been stored at 4° C. and 0.1 and 1.0 ml. were added to pour plates of tryptose-glucose agar. Counts were done after 24 hours' incubation at 37° C.

3. All plates showing no growth after 24 hours were incubated for an additional three days before being pronounced negative. There is some controversy regarding significant colony counts. Merritt<sup>5</sup> states that 50,000 bacteria per ml. is significant, but most other authors accept 100,000 per ml. as the point at which a differentiation from contamination should be made. We have used 100,000 per ml. as the critical point for this study.

#### RESULTS

#### 1. Age Factors

In the postmenopausal group, the age distribution, age at menopause and number of years since the menopause (Tables I-III) show no remarkable features except for five women ostensibly still menstruating at age 56.

TABLE I.—AGE DISTRIBUTION OF POSTMENOPAUSAL PATIENTS BY DECADES

Decade	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	80 -
Number	2	18	27	28	18	7

#### TABLE II.—AGE AT MENOPAUSE

Age	30 - 39	40 - 45	46 - 49	50 - 55	56 +	Not known
Number	10	20	24	34	5	7

#### TABLE III.—YEARS POSTMENOPAUSAL

Less than 3	4-6	7 - 10	11 - 15	16 - 20	20+	Unknown
27	5	15	16	8	22	7

No age breakdown was attempted in the premenopausal patients, because age was not considered to be a significant factor.

#### 2. Previous Gynecological Surgery

Previous gynecological surgical procedures to which the patients in this investigation were subjected are shown in Table IV. The procedures listed are those which directly or indirectly might lead to urinary tract trauma, either in the nature of the operation or because of catheterization. Forty per cent of the postmenopausal patients had such procedures, but only one of these had a

<sup>\*</sup>From the Department of Obstetrics and Gynecology, Jewish General Hospital, Montreal.

TABLE IV.—Previous Gynecological Surgery. (Cervical Polypectomy or Adnexal Procedures are Excluded.)

Type of surgery	Premenopausal	Postmeno pausal
Dilatation and curettage.	2	7
D & C with AP. repair D & C, AP. repair,	1	0
fistula repair	0	1
D & C and radium	0	1
Excision of caruncle	0	1
AP. repair	1	5
Vaginal hysterectomy Vaginal hysterectomy with	0	2
AP. repair	0	2
Removal cervical stump	0	1
Abdominal hysterectomy. Abdominal hysterectomy	0	16
with later AP. repair	. 0	3
Ventral suspension	1	0

significant colony count. In the premenopausal group, 24% had previous gynecological surgery but none of these had a positive colony count. Therefore, previous gynecological surgery does not appear to be a significant factor,

#### 3. Positive Urological History

By history alone 38% of the premenopausal patients and 57% of the postmenopausal patients had urinary tract complaints, recent or remote, which are listed in Table V. Except for stress incontinence, the type and frequency of the complaints in the two groups are comparable. Of the postmenopausal patients with significant colony counts all but one had urinary symptoms and that one had had a previous anterior repair. In the premenopausal group one of the two patients who had a positive urine examination had symptoms.

TABLE V.—Positive Urological History

Symptom	Premenopausal	Postmenopausal
Dysuria	13	22
Nocturia	22	22
Frequency	15	13
Urgency	1	2
Suprapubic pressure	5	4
Pressure in urethra	0	1
Stress incontinence	1	11
Difficulty in starting	0	3
Previous cystitis	2	0
Previous cystotomy	1	0
Hematuria	0	1
Albuminuria	0	1
Nephrectomy	1	1
	38 cases	57 cases

#### 4. Pelvic Findings

The physical findings revealed by pelvic examination are shown in Tables VI and VII. Cervicitis and vaginitis are about equally distributed, but marked pelvic relaxation, especially in the form of cystocele and prolapse, is much more common in the postmenopausal group. The importance of this in the light of bacterial counts will be discussed later.

TABLE VI.—Pelvic Findings—Premenopausal Patients

Normal				. ,					 										26
Leukorrhea										*			*				*		6
Vaginitis																			3
Cervicitis.									 										17
Cervical po	ly	).															*		2
Cystocele.																			
Rectocele.																			(
Pregnancy.																			29
Fibroids																			7
Pelvic infla																			8
Hydatidifor	m	n	10	ole	e.													,	1
Adnexal pa	the	ole	20	r.															(

TABLE VII.
PELVIC FINDINGS—POSTMENOPAUSAL PATIENTS

Normal	22
Vulvitis	11
Vaginitis	17
Cervicitis	12
Cystocele	27
Rectocele	21
Caruncle	15
Prolapse	7
Cervical polyp	4
Vault granulation	2
Atrophia muses	10
Atrophic mucosa	2
Carcinoma of cervix	1
Sebaceous cyst of vulva	1
Vulvar hemangioma	1
Vaginal polyp	2
Fibroids	7
Adnexal mass	2
Pelvic inflammatory disease	1

#### BACTERIOLOGY

Sterile cultures were obtained in 49% of the premenopausal patients and 30% of the postmenopausal patients. The flora obtained in the two groups are shown in Table VIII. Of the major pathogenic bacteria, only *E. coli* and *Aerobacter aerogenes* were found more frequently in the postmenopausal patients. There were only two patients in the premenopausal group with urinary tract infection, the bacteria responsible being *E. coli* and *A. aerogenes*. In the postmenopausal group, there were seven with positive culture, three of which were due to *E. coli*, three to *A. aerogenes*, and one to combined *E. coli* and *A. aerogenes* infection. If Merritt's<sup>5</sup> criterion for significant bacteriuria is used, there were three positives in the premeno-

TAPLE VIII.—BACTERIAL FLORA

Type of bacteria	Premenopausal	Postmenopausal
Enterococcus	4	9
Micrococcus	7	9
Streptococcus sp	15	8
Strep. viridans	2	4
Strep. fecalis	0	<b>2</b>
B-hemolytic strep	3	$\frac{2}{2}$
Staph. pyogenes	3	3
Microaerophilic		
hemolytic strep	2	0
E. coli	1	5
A. aerogenes	4	8
Proteus		3
Pseudomonas	1	ŏ
Hemophilus	Ô	ĭ
Corynebacterium	Ď.	î
Candida	0	1
Diphtheroids	13	8
Bacterioides	0	1

pausal group and eight in the postmenopausal group. Application of the Chi-square test shows that neither of these findings is statistically significant. It is an interesting observation that the colony count in both premenopausal cases was less than 200,000 while six of seven of the postmenopausal positives were over 1,000,000 and the seventh was almost 5,000,000. The significance of this, if any, is not known.

#### EFFECT OF PELVIC RELAXATION

A breakdown of the cases with pelvic relaxation is shown in Table IX. As expected, there is a much higher incidence of cystocele and procidentia in the postmenopausal group. Also, the incidence of

TABLE IX.—Effect of Pelvic Relaxation

Premenopausal patients:			
Cystocele			5%
Procidentia			0
Postmenopausal patients:			
Cystocele			27%
Cystocele Prolapse			7%
Total			34%
Postmenopausal patients wi	th posi	tive urine speci	mens:
Cystocele			28.6%
Cystocele Procidentia			42.9%
Total			71.5%

cystocele and procidentia is extremely high among postmenopausal patients with positive urine examination, but neither of the two premenopausal patients with positive urine cultures showed pelvic relaxation.

#### DISCUSSION

In this pilot study, an attempt has been made to determine whether there is any difference in the incidence of significant bacterial growth in the urines of patients before and after the menopause. The author assumed, before the study, that there might be some difference because of poor vaginal and cervical resistance to local infection owing to reduced estrogen levels, and the existence of lymphatic communications between cervix, vagina, urethra and trigone. However, the results show no statistically significant difference between the two groups in this study. There is some numerical difference, and possibly if five or ten times as many cases were investigated by the same procedures, some significant statistical difference would appear. The assumption may be correct for a different reason. The high incidence of cystocele and procidentia among the postmenopausal cases with positive urines suggests that the significant factor may be structural instead of endocrine.

The postmenopausal patients with significant colony counts have been placed on estrogens in an attempt to clear the urine without the use of antibiotics. The results of this investigation, which will be reported in a subsequent communication, may influence the concept that low estrogen levels increase susceptibility to bacteriuria in the postmenopausal patient.

Kass, Miall and Stuart<sup>7</sup> have repeatedly stressed the importance of significant bacteriuria as a cause of long-term cardiovascular-renal damage. All possible avenues should be investigated in an attempt to reduce this important cause of chronic disease.

#### SUMMARY

One hundred premenopausal and 100 postmenopausal women had examinations of the urine obtained with a catheter in an attempt to discover whether there was any difference in either the bacterial flora or the number of cases with positive colony counts in each group. No statistically significant difference could be found between the two groups. It would appear that pelvic relaxation is the major factor accounting for any difference noted. The possible role of estrogens is also discussed and is under further study.

The author would like to express his appreciation to Drs. Leighton Smith and Harold Baker of Ayerst Laboratories and to Ayerst Laboratories for their co-operation in per-forming the bacteriological studies. A debt of gratitude is owed the nurses in the outpatient department for their kind co-operation.

#### REFERENCES

- KASS, E. H.: Am. J. Med., 18: 764, 1955.
   REICH, W. J., WILKEY, J. L. AND NECHTOW, M. J.: Urol. & Cutan. Rev., 51: 82, 1947.
   WINSBURY-WHITE, H. P.: Brit. J. Urol., 2: 165, 1932.
   MARPLE, C. D.: Ann. Int. Med., 14: 2220, 1941.
   MERRITT, A. D. AND SANFORD, J. P.: J. Lab. & Clin. Med., 52: 463, 1958.
   KASS, E. H.: Tr. A., Am. Physicians, 69: 56, 1956.
   KASS, E. H., MIALL, W. E. AND STUART, K. L.: J. Clin. Invest., 40: 1053, 1961.

#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Search into the records of the Winnipeg General Hospital search into the records of the Winnipeg General Hospital has given material for two interesting papers. One of these, "Typhoid in the Winnipeg General Hospital," was published in the June number of this Journal. In a paper recently read before the Winnipeg Medico-Chirurgical Society, Dr. Mitchell finds that from 1883 to 1910, twenty-two cases of aneurysm were recorded in the Winnipeg General. From 1892 to 1909, inclusive, there were eighteen cases amongst fifty-one thousand and sixty-nine patients, or one to two thousand eight hundred and thirty-seven. In sixteen cases the age was mentioned, the average being 82.87 years,-in close accord with the statistics of various investigators. Of these sixteen, fifteen were males. In the histories of six, two aneurysms were the result of syphilis, and five were associated with an excessive use of alcohol. The site of the aneurysm in eighteen cases was: aorta, nine; popliteal, two; femoral, three; posterior tibial, two; innominate, one; cirsoid aneurysm of the scalp, one.-Canad. M. A. J., 1: 890, 1911.

# THE RELATIONSHIP BETWEEN THE DOSAGE OF ATROPINE AND THE EFFECTS ON REFLEX PAROTID SECRETION AND HEART RATE IN MAN\*

W. C. STEWART, M.A., M.D.† and HELEN CURRIE,‡ Ralston, Alta.

ATROPINE sulfate is customarily injected into patients about to undergo general anesthesia, to reduce secretions of glands in the upper respiratory tract and also to block cardio-inhibitory reflexes mediated through the vagus nerves. Mushin, Galloon and Lewis-Faning<sup>1</sup> found that subcutaneous injection of 0.65 mg. (1/100 grain) of atropine sulfate caused an inhibition of total reflex salivation in humans, but the inhibition was less than 50% complete and of rather short duration. There appears to be little information available to define the relationship betwen the injected dosage of atropine and the degree of suppression of the salivary reflex. Extensive studies have been made on the effect of atropine in suppressing salivation stimulated by injection of parasympathomimetic drugs.<sup>2-5</sup> However, since in these experiments the atropine was administered intravenously, and salivation was induced by drugs rather than through reflex nervous pathways, there is some doubt that the results would apply quantitatively in the usual clinical application of the drug.

The experiments to be described were motivated by an interest in the pharmacology of atropine, particularly when injected intramuscularly at the higher doses contemplated for military use in the treatment of nerve gas poisoning.

#### **METHODS**

Parotid secretion was collected through a suction cup applied to the opening of the parotid duct, by a technique described by Hildes and Ferguson.6 To stimulate the secretion of saliva, small volumes of lemonade were pumped into the mouth through a fine tube. The flow of lemonade was intermittent rather than continuous, because intermittent stimulation appeared to give more sustained and reproducible rates of salivation. Commercial frozen lemonade was made up according to the manufacturer's directions, and allowed to flow from a reservoir by gravity. The flow was controlled by an electric hoselock and timer adjusted to deliver 2 ml. of lemonade over about ten seconds. The deliveries were separated by intervals of 110 seconds during which the flow was stopped. The parotid saliva was collected in a graduated tube, and the accumulated volume was estimated at regular intervals of 8.5 minutes. At the same time the heart rate was recorded, using a stethoscope and stop-watch.

Nine volunteers were used in the investigation, each volunteer submitting to the experimental procedure twice, once on each of two different days. On each occasion the subject was supported in a semi-reclining position in bed. The suction cup was applied to the parotid duct, the flow of lemonade was started, and as soon as the outflow tube was seen to be filled with saliva the first observation period commenced. After three observation periods of 8.5 minutes had passed, an intramuscular injection was given, either of atropine sulfate or of saline. The subject was not told which injection he received, although all volunteers understood in advance the general plan of the experiment, and the nature of the drug and dosages to be used. Observations of salivary flow and heart rate were continued for nine observation periods (76.5 minutes) after the injection.

The nine volunteers thus provided nine pairs of experiments, each pair made up of a control in which an injection of saline was given, and an exactly similar experiment in which the same subject received a dose of atropine sulfate. Because the observations were timed exactly with respect to the instant of the injections, control and experimental data could be compared at various time intervals after administration of atropine.

Of the nine volunteers, three were given a low dose of atropine sulfate (0.5 mg. per 70 kg. of body weight), three an intermediate dose (1.0 mg./70 kg.), and three were given the highest dose (2.0 mg./70 kg.). (The dose which has been adopted for first-aid treatment of nerve gas poisoning is 2.0 mg. per man, regardless of weight.) This range of doses was adopted in order to bracket the "usual clinical dose" of 1/100 grain (0.65 mg.) per person, and to facilitate statistical computations. The selection of the particular dose to be given to a volunteer was made by use of a table of random numbers. The dosage of atropine was proportioned to the body weight by varying the volume of the injection: in this way both the amount of atropine and the volume of the injection were proportional to the body weight.

#### RESULTS

Two sets of observations were obtained from each volunteer, one set from the atropine experiment and one set from the control experiment in which saline was injected. Each set was made up of 12 observations of parotid secretion rate averaged over the previous 8.5-minute collection period, and 12 estimations of heart rate taken at the end of the collection interval.

#### Rates of Parotid Secretion Before Injection

In each atropine experiment three observations of reflex parotid secretion rate were made before

<sup>\*</sup>Contribution from the Suffield Experimental Station of the Defence Research Board of Canada, Ralston, Alberta, as Technical Paper No. 214. DRB Project No. D52-89-50-15. †Physiology Section, Suffield Experimental Station, Ralston, Alberta. †Medical student, Queen's University, Kingston, employed at Suffield Experimental Station during the summer of 1959.

the injection of the atropine: similarly in the control experiments three observations were taken before the injection of saline. These figures afforded an opportunity to estimate the variation of flow rates between individuals, within individuals on different occasions, and within a single experiment. The three flow rates observed before the injection in each of the eighteen experiments are shown in Table I.

TABLE I.—RATES OF REFLEX PAROTID SECRETION IN NINE VOLUNTEERS

	S	aliva	tion i	rates	(ml.	× 10	100/min.		
	Ex	perin	ient	Ex	perin	Volunteer			
Volunteer		1			2	means			
JGM	26	31	13	13	18	23	20.7		
WAL	5	7	4	4	10	8	6.3		
SMB	99	69	90	86	70	78	82.0		
MRG	40	54	53	46	49	47	49.7		
JDC	11	13	19	8	17	5	12.2		
BMM	23	23	22	23	26	23	23.3		
DWG	47	40	49	30	31	34	38.5		
WEA	30	45	23	18	33	36	30.8		
JHP	19	1	16	13	17	20	14.3		

The analysis of variance of these data is shown in Table II.

TABLE II.—Analysis of Variance of Rates of Reflex Parotid Secretion

Source of variance	Degrees freedom	Sums of squares	$Mean \\ square$	F ratio
Replicate observations (3)	2	13	6.5	
Volunteers (9)	8	26,146	3268	49.2
Error term for volunteers				
$(3-1) \times (9-1)$	16	1063	66.4	
Experiments	1	137	137	3.4
Interaction: Volunteers $\times$ experiments (9-1) $\times$ (2-		376	47	1.2
Error term for experiment 9 (2-1) (3-1)	s 18	720	40	
Total	53	28,445		

The large variance for the difference between volunteers is highly significant statistically, and shows that the great differences in reflex salivation rates observed were real and reproducible differences between individuals when tested by the technique described. On the other hand, flow rates for a single individual taken on different days varied no more than successive observations within a single experiment, a comparison which confirms the reproducibility of results obtained in this way.

#### Effect of Atropine on Reflex Parotid Secretion

To show the effects of the various doses of atropine sulfate on reflex parotid secretion, mean flow rates at each of the three dosages of atropine are plotted against time in Fig. 1.

The set of results observed at 34 minutes after the injection was taken for statistical analysis, because at that time the effect of atropine was apparently at a maximum. For each volunteer, the flow rate at 34 minutes in the atropine experiment

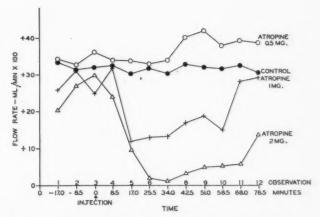


Fig. 1.—The effect of graded doses of atropine sulfate on parotid secretion rates. In the line marked "control", each point is the mean of control observations on all nine volunteers. All other points represent mean values for three volunteers.

was subtracted from the flow rate at the corresponding time in the control experiment. The difference so obtained was then expressed as a percentage of the control flow rate for that individual at that time. The resulting figure represents the percentage inhibition of reflex salivation 34 minutes after the injection of atropine. The data are shown in Table III.

TABLE III.—PAROTID SECRETION RATES 34 MINUTES AFTER INTRAMUSCULAR INJECTION OF GRADED DOSES OF ATROPINE SULFATE

	Atropine		ecretion rates 100/min.)	Atropine	Per cent
Volunteer	dose (mg./70 kg.)	After saline	After atropine	effect $(ml. \times 100/min.)$	of secretion
JGM	0.5	22	16	6	27
WAL	0.5	5	5	0	0
SMB	0.5	78	82	-4	-5
MRG	1.0	54	34	20	37
JDC	1.0	10	2	8	80
BMM	1.0	20	4	16	80
DWG	2.0	51	2	49	96
WEA	2.0	14	2 2 0	12	86
JHP	2.0	17	0	17	100

The apparent relationship between the dose of atropine and the percentage of inhibition of salivation was subjected to statistical analysis by the method described by Bliss.<sup>7</sup> The result of this analysis is shown in Table IV.

TABLE IV.—THE EFFECT OF ATROPINE ON SALIVATION ANALYSIS OF VARIANCE OF THE DOSE-RESPONSE REGRESSION

Source of variance	Degrees freedom	Sums of squares	$Mean \\ square$	F ratio
Slope of the regression line Scatter of dose means abo		11,267	11,267	25
line (non-linearity)	1	450	450	1.4
Remainder (error term)	6	1929	321	
Total	8	13 646		

The variance shown in Table IV for the slope of the regression effect on log dose is highly significant statistically, thus attesting to the reality of the relationship. The small size of the "non-linearity" variance shows that within the limitations of the experiment the relationship between log

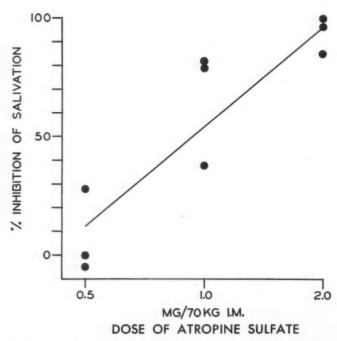


Fig. 2.—Percent inhibition of salivation, 34 minutes after intramuscular injection of atropine sulfate. Each point represents the difference betwen control and atropine experiments in one volunteer.

dose and response was not discernibly curved. However, it must be assumed that the relationship would not be linear through the range of all possible doses, and that non-linearity would become apparent if sufficient data were collected.

In Fig. 2 the percentage of inhibition of reflex salivation at 34 minutes after injection has been plotted against the dose of atropine, along with the calculated regression line.

#### The Effect of Atropine on Heart Rate

The observations of heart rate were changed into figures representing the increase from that seen before the injection of either atropine or saline. To make this transformation, the following steps were taken:

1. In each experiment the first three observations of heart rate, those made before the injection, were averaged to the nearest whole number of beats per minute.

2. This mean initial number of beats per minute was then subtracted from each of the 12 observations in the experiment. This gave a series of 12 positive or negative numbers, representing the change from the mean initial heart rate.

3. For each pair of experiments, the figure obtained at a given time in the control experiment was subtracted algebraically from the corresponding figure in the atropine experiment. This reduced the data to nine sets, each of 12 numbers, representing the increase in heart rate caused by atropine.

The mean increases in heart rate are shown plotted against time in Fig. 3.

The set of heart rate observations taken 42.5 minutes after the injections appeared to show

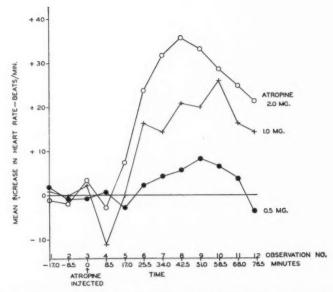


Fig. 3.—Increase in heart rate after intramuscular injection of atropine sulfate. Each curve represents mean values for three subjects.

maximal differences between dosage levels, and statistical analysis gave essentially similar results to those obtained from the salivation data, except that the mean square for the regression reached only the 5% level of significance. The calculated regression line and the observed points are plotted in Fig. 4.

#### DISCUSSION

Although the number of subjects used in this study was small (nine persons), the use of a complete control sequence in a crossover design considerably reduced the uncontrolled variation. Exactly similar experiments on reflex parotid secretion

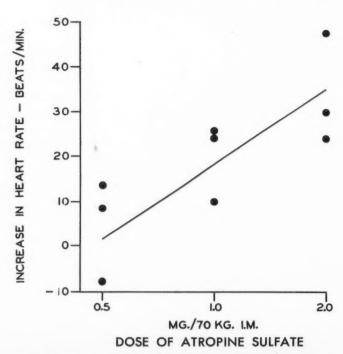


Fig. 4.—Increase in heart rate, 42.5 minutes after intramuscular injection of atropine sulfate. Each point represents the difference between control and atropine experiments in one volunteer.

apparently have not been done previously, although there have been comparisons of the effects of certain doses of atropine with certain doses of other drugs used for suppressing salivary secretion.1-5

The results obtained here agree essentially with those of Mushin, Galloon and Lewis-Faning1 which indicated that injected doses of atropine sulfate of 0.65 mg. caused less than 50% suppression of reflex salivation. It seems safe to conclude that, in young adults given atropine sulfate intramuscularly, a dose of 2 mg./70 kg. may be expected to depress reflex salivation severely for about one hour or slightly longer. This dose also causes a pronounced but variable increase in heart rate which lasts somewhat longer than the salivary inhibition.

Intramuscular injection of 1 mg./70 kg. may be expected to cause partial suppression of reflex parotid secretion lasting about 3/4 hour, accompanied by smaller increases of heart rate than seen after the higher dose. These changes in heart rate are similar to those observed by Taylor et al.8 in a larger group, after injection of a total dose of 1.5 mg. per person regardless of body weight.

Doses of atropine sulfate of 0.5 mg./70 kg. or less are unlikely to cause any useful degree of suppression of reflex parotid secretion or vagal blockade.

#### SUMMARY

Reflex parotid secretion and heart rate were measured in nine volunteers at intervals before and after injection of graded doses of atropine sulfate, ranging from 0.5 to 2.0 mg. per person. Effective inhibition of the salivary reflex and vagal blockade were observed after doses of 2.0 mg. of atropine sulfate per 70 kg. of body weight. Doses of 0.5 mg. per 70 kg. were almost completely ineffective. Doses of 1.0 mg. per 70 kg. caused about 50% inhibition of reflex parotid secretion which lasted not longer than about 45 minutes.

The authors gratefully acknowledge the co-operation of the volunteers who took part in these experiments. Thanks are also expressed to the Defence Research Board of Canada, for permission to publish this paper.

#### REFERENCES

- Mushin, W. W., Galloon, S. and Lewis-Faning, E.: Brit. M. J., 2: 652, 1953.
   Galloon, S.: Brit. J. Anaesth., 28: 113, 1956.
- 3. NYMAN, E.: Acta physiol. scandinav., 3 (supp. 10): 1-127,
- DIAMANT, B., DIAMANT, H. AND HOLMSTEDT, B.: Arch. internat. pharmacodyn., 111: 86, 1957.
- 5. WYANT, G. M. AND DOBKIN, A. B.: Anaesthesia, 12: 203, 1957.
- HILDES, J. A. AND FERGUSON, M. H.: Canad. J. Biochem. & Physiol., 33: 217, 1955.
- BLISS, C. I.: The statistics of bioassay, Academic Press Inc., New York, 1952.
- 8. TAYLOR, W. J. et al.: Canad. M. A. J., 82: 1147, 1960.

#### CANADIAN JOURNAL OF SURGERY

Volume 4, No. 5 issue of the Canadian Journal of Surgery will be published in October 1961. Subscription rates to the Canadian Journal of Surgery are \$10.00 per year for four issues or \$2.50 for a single copy.

The October 1961 issue will contain the following original articles, case reports and experimental surgery:

Original Articles: Etude clinique de 238 cas d'endométriose chirurgicale—B. Lambert, P. Meunier et C. Ouimet. The problem of late local recurrence of carcinoma of the cervix—J. P. A. Latour and W. D. Fraser. Hypertensive reaction following resection of coarctation of the aorta-R. K. Padhi, E. M. Nanson and R. B. Lynn. Surgical experience in resection of aneurysms of the thoracic aorta—P. Allen, R. Robertson, W. G. Trapp and W. A. Dodds. Thoracic sequestration cysts of fetal bronchogenic and esophageal origin—G. B. Elliott, G. E. Miller, R. H. Walker and K. A. Elliott. Nitrogen mustard in treatment of metastatic carcinoma of the testis—G. J. Ankenman and J. Balfour. Epithélioma colloïde du sein-R. Tremblay et J.-L. Bonenfant. Preauricular sinus-J. A. McLachlin and R. O. Farley. Primary basilar impression of the skull—H. F. W. Pribram and R. J. Porter.

Case Reports: Splenic aneurysm—R. E. Pow, G. B. Elliott and B. Freigang. Two synchronous primary malignant tumours (kidney and colon)—T. S. Wilson. Mesenchymoma in the retropubic space—C. Schneiderman, M. A. Simon and M. M. Gelfand. Thymic cysts of the neck—R. Côté and C. Fortin. Rupture of aortic aneurysm into duodenum: a successfully treated case—W. A. Maclean and C. M. Couves.

Experimental Surgery: The etiology and pathogenesis of cholecystitis: an experimental study—D. J. Currie. Some observations on peripheral blood flow, blood gas, and electrolyte content of the dog's limb after sympathectomy-R. K. Padhi and R. B. Lynn. Splenic and bone marrow homografts in the dog after lethal body irradiation-J. W. Irvine and S. Kling.

# THE CHOICE OF TREATMENT IN FRACTURES OF THE FEMORAL SHAFT IN ADULTS\*

JOHN W. MARTYN, M.D. and PAUL F. McGOEY, M.D., Toronto

THE AUTHORS commenced this study with the hope that definite conclusions might establish a policy for this large teaching hospital. A previous review of adult hip fractures supported the method of primary definitive operative treatment as a life-saving measure in the older age group. A more conservative approach is necessary when dealing with fractures below the trochanteric level.

#### INCIDENCE

It was necessary to go back ten years to obtain 100 consecutive cases for study. During the same period more than 700 patients with fractures of the hip were admitted to St. Michael's Hospital,

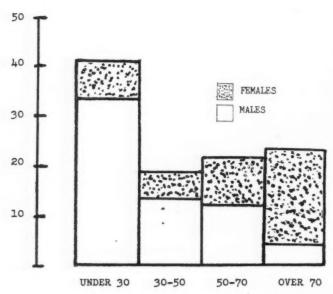


Fig. 1.-Age and sex incidence in femoral shaft fractures.

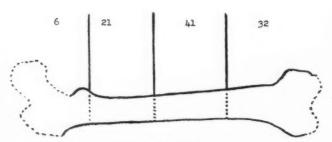


Fig. 2.-Incidence of fractures and their levels.

Toronto. Fractures of the femoral shaft were more common in men owing to the weighting of this series with industrial injuries. There was a preponderance of females in the older age groups (Fig. 1). Fig. 2 shows the level of these fractures. Six patients who

#### THE MECHANISM OF INJURY

As expected, traffic and industrial accidents were more common in the younger age groups, home accidents more prevalent among the aged. The increased hazard of ice during winter seemed to be offset by the tendency for people to stay indoors, thereby eliminating a seasonal incidence. Alcoholism was a factor in the accidents which occurred to 11 of these patients. Seven pathological fractures were included: two men had secondary prostatic carcinoma; four women had secondary deposits from carcinoma from the breast; and one patient had Paget's disease.

#### TREATMENT

Sixty-four patients had associated problems and these are summarized in Table I. The importance of associated injuries and diseases must be emphasized in the total management of these patients. These problems received detailed attention concurrently with the treatment of the femur. In sharp contrast with experience gained in the hip series, the authors were impressed with the value of "staged" treatment. Primary splinting with traction by skeletal pin transfixion below the tibial tuberosity was instituted in the emergency room

TABLE I.—PRE-TREATMENT PROBLEMS

Other fractures			. ,		,			25	
Cardiovascular disease								15	
Acute alcoholism								11	
Pulmonary disease								8	
Genitourinary conditions								4	
Diahetes								1	

and a Thomas splint was applied with the administration of local anesthesia and sedation in most cases. The house officers were instructed to search for other injuries. Secondary treatment with open reductions and intramedullary nailing was necessary in 46 cases.

The cardiac status of patients in the older age group required close co-operation with the medical specialists. Myocardial ischemia or failure and pulmonary disease were the major medical problems. Eleven patients with severe alcoholism created the most difficult problems in early management, and despite intensive care this small group provided a high percentage of the postoperative complications shown in Table II. Delirium tremens per se was not mentioned as a complication but was a cause of mistaken diagnosis on several occasions, particularly in reference to fat embolism. The

had long fractures that extended from the trochanteric area distally were considered separately because they represent an area of overlap with the previous review of hip fractures. In fact, only one of these six patients could be treated by a combined pin and long plate unit without traction or intramedullary fixation.

<sup>\*</sup>From the Department of Surgery, St. Michael's Hospital, Toronto.

TABLE II.—Postoperative Complications

Infections in fracture wound	3
Infections in tibial traction pin	10
Pulmonary	8
Urological	. 7
Fat embolism	2

latter condition was readily diagnosed in two patients who had petechial hemorrhages in addition to the usual pulmonary and cerebral manifestations. A patient suffering from chronic alcoholism with malnutrition and edema, as well as heart disease, presented a difficult problem in general management on at least one occasion.

#### MORTALITY

The seven deaths in this series included three patients who died from secondary carcinoma of the brain from a primary site in the breast. Two patients died suddenly from episodes which were diagnosed as coronary thrombosis despite the more likely possibility of pulmonary embolism. One patient exsanguinated during massive hemorrhage from a gastric ulcer on the fifth day after an open reduction, All the deaths and most of the complications occurred in patients over 65 years of age (Table III).

#### TABLE III.—CAUSE OF DEATH

Carcinoma of breast							3
Myocardial infarction							2
Cerebrovascular accident							1
Hemorrhage from gastric ulcer							
(D. 4. 1						_	_
Total							6

#### DISCUSSION

The elementary principle which states that the doctor should "obtain and maintain an anatomical position that will yield optimum function with a minimum of pain, effort and expense" is tested to the utmost in the management of adult femoral fractures. Basic statistics pertaining to mortality and morbidity tell only a small part of the whole story. Quite apart from the anatomical features of the fracture and the general condition of the patient, the decision regarding the choice of treatment may tax the best judgment of the surgeon and facilities available to him.

Our experience suggests that traction is well tolerated in the younger age groups. Furthermore, the anatomical and functional results are very good when the necessary degree of skill is used. When Küntscher's² method was introduced, the German army was operating on a "fluid eastern front" and a method which permitted early fixation and the speedy evacuation of numerous casualties was of great value. This was readily appreciated by those in military service who had to remain beside patients tethered in bed by a traction apparatus during enemy attacks. The "Tobruk" splint and transfixion pin fixation methods were used by the

Allies in the more active battle areas. The popularity of the rediscovered and improved intramedullary fixation method may not stand critical scrutiny in peacetime civilian practice. Indeed the recent enthusiastic statements of Küntscher<sup>3</sup> pertaining to his technique might encourage some surgeons to fit too many patients to the method, the Procrustes concept in Greek mythology. We have shared the grief of many in discovering that a transverse upper shaft fracture with a flexed and abducted proximal fragment in a young adult with a thick cortex is a different problem from the comminuted osteoporotic shaft of his grandmother. Furthermore, in both patients the ultimate prospects for the return of knee function are inversely related to the degree of soft tissue involvement and the distance of the fracture from the hip, presuming that diligent aftercare is given. The argument that the Küntscher nail allows early ambulation towards the exit door must be balanced against the quality of the aftercare arrangements. On the other hand, we have found it increasingly difficult to train house surgeons and nurses in the traction care needed by patients with this somewhat rare injury and one can readily appreciate the wisdom of concentrating such patients for the purpose of special treatment.

There is less urgency about primary definitive operative treatment for many patients with femoral fractures. We have been unable to find any significant difference in the end results obtained from traction or operative treatment, except for the longer hospital stay in the traction group. On the other hand, we have had occasional unfortunate experiences during the aftercare of patients with Küntscher nails. The authors believe a personal selection of the best method must be made for the primary treatment of these cases. An alternative or combined method may be used later. We prefer rigid intramedullary fixation to the use of plates or screws in delayed union or non-union and in suitable pathological fractures.

While restricted knee movement is no longer a serious problem in high fractures, it has been troublesome at a lower level in six patients treated in traction and six treated by operative methods. Supervised active knee movement can be started early with either method. The hazard of disturbing the fracture area is very real in overly enthusiastic efforts "to get the knee going". The responsibility of avoiding such hazards should be shared by all members of the treatment team at each stage of progress. The attending surgeons should assess the patient carefully before allowing him any initiative and responsibility in the early stages of union. The Hansen-Street nail was discarded because of difficulties encountered in four patients and we have used vitallium Küntscher nails exclusively during the past five years. Occasionally a plaster hip spica was combined with intramedullary nailing in unstable fractures during the first few weeks.

Urological complications occurred in seven patients treated in traction; four women had minor infections and one man developed a "recumbency calculus". Antibiotics were administered to 71 patients at some stage of treatment. As one would expect in peacetime injuries, compound fractures were exceedingly rare and there were only seven infections of the fracture area. There were three moderately severe traction pin infections, none of which was refractory to treatment, but these infections necessitated an additional month in hospital on the average.

The house staff were particularly cautious about "over-pulling" the fractures treated by traction. During the first few days repeated measurements, in order to keep the affected leg a shade shorter than its opposite member, reduced the need for frequent radiographs. The use of the knee flexion hinge helped to simplify the control of rotation, and every effort was made to obtain an anatomical position consistent with good function during the first few days. General anesthesia was seldom necessary to reduce the fractures of patients treated in traction.

Children and young adults tolerate traction very well. When undergraduates are taught that conservative treatment with traction is the method of choice in this age group, we should be prepared to answer the question "What are the other choices if the position obtained by the tenth day is unsatisfactory?"

In almost all cases where operative treatment was chosen to replace traction, the decision was made after discussion with the consulting staff before the 15th day. This policy yielded good anatomical results except for shortening in one case, a refracture in another and the infections previously mentioned. In the entire series there

was only one instance of delayed union, and the problem of non-union was avoided by the use of primary bone grafting from the adjacent iliac crests or early secondary bone grafting when the attending staff felt that the rate of union was slow.

#### MORBIDITY

The average stay in hospital was 108 days for 45 patients treated in traction and 58 days for the 46 patients who were treated by operative methods. Only 22 patients were transferred to convalescent hospitals, before going home.

#### SUMMARY

While the study appears to support the use of operative methods of treatment in fractures of the femoral shaft to conserve hospital beds, the authors believe that such a policy requires careful collaboration of a highly skilled staff with excellent facilities to cover all phases of treatment. Geographical and seasonal factors in Canada may make it awkward to move patients with femoral fractures in many cases. The 1956 census reveals that most of our aged people live in larger cities and warmer climates. This is the age group that constitutes the crux of the problem. All the deaths and most of the complications occurred in people over 65 years of age.

The authors realize the fallacy of drawing conclusions from a small series. The difficulties involved in accumulating a large series of fractures of the femoral shaft may explain why there are so few papers on this subject in the Canadian medical literature and why some of the problems in this field have remained unanswered.

#### REFERENCES

- McGoey, P. F. and Evans, J.: Canad. M. A. J., 83: 260, 1960.
- 2. Küntscher, G.: Zentralbl. f. Chir., 67: 1145, 1940.
- 3. Küntscher, G. B.: J. Bone & Joint Surg., 40A: 17, 1958.

#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

#### JAMES COOK

For many years past when two graduates from the medical faculty of McGill University met together and began to discuss college affairs the first question usually was, "How is Cook?" Cook was the janitor; and now he is dead. Only those who were brought up in that school will understand why the death of so humble an official should receive formal mention in these pages . . .

He was more than a janitor: he was a tradition. He fulfilled the function of a janitor by being a janitor, as a professor fulfils the function of professor by being a professor. To have achieved a place of affection and respect in the hearts of thirty-five generations of medical students was a rare feat: he accomplished it by his great humanity and his confidence in himself as essentially a man.

Did any medical student attempt "to put it over him," he had seen medical students of equal promise bowed and broken in far-off spring-times. Did any student add to the gaiety of youth an artificial exuberance, he had many times shaken his wise old head over those formal notices which appear so regularly in the newspapers. Was any one too clever, he had seen many clever students return to wander about the buildings and none but himself to know their names. He looked unmoved upon the student of the fourth year, upon the popular young demonstrator, upon the marvelous lecturer newly arrived from foreign parts, even upon professors and deans, because he had witnessed their passing from generation to generation. Like the filius terrae in the old academic convocations, he was ever at the ear to remind the most honoured ones by gibe and jest that all human greatness is destined to perish. Of the freshmen he was tolerant without contempt, because many of the most celebrated physicians in Canada had once been freshmen in his hands. If he was kinder than he seemed, probably he was not so wise as he seemed to be. No mere man could be; but he presented an appearance of wisdom which appalled even if it did not convince.—Canad. M. A. I., 1: 888, 1911.

#### MEDICAL ECONOMICS

#### HEALTH INSURANCE IN **AUSTRALIA**

T. J. QUINTIN, M.D., Sherbrooke, Que.

IN APRIL 1778 Captain James Cook re-read his secret instructions from the Admiralty, which told him, "There is reason to imagine that a continent or land of great extent may be found to the Southward of the track of former navigation." This eastern part of Australia, which Cook discovered, is now the centre of population density. Australia today, despite its size-it is larger than all Europe, excluding Soviet Russia, and almost the same size as the U.S.A.-is an urban country, with half of its population in the six state capitals and only a third truly rural. This division of population is the result of the difficulties of inland development and is not due to any failure to try to settle "out-back". Australia is young, younger than Canada, yet somewhat similar to Canada in concentration of population and in the effect of extremes of temperature on population and economy.

To understand and appreciate the Hospital Insurance Scheme of Australia it is necessary to know something of the Australian. A. G. L. Shaw says, "This is the century of the common man and perhaps in Australia he attained his goal earlier than in many other countries. Without a governing class they have been on the whole well governed. They have been the pioneers of much social reform, particularly in the realm of industrial relations.' They are individualistic and yet are ready to band together to form a strong labour movement. The Friendly Societies which they brought with them from England were strongly organized and well developed in the first half of the Nineteenth Century. Dr. W. R. Pugh, the father of anesthesia in Tasmania, organized the first prepaid medical scheme in Launceston in 1847. His fee schedule, apparently for complete medical coverage, was sixpence per week for married couples and threepence for single persons. If admitted to the local hospital which the doctor established, the patient was charged two shillings per day. Dr. Pugh and his assistant Dr. Grant rendered their services free. This was the beginning of the "honorary system". So the idea of having the patient share the cost of his illness was established early in Australia.

In the practice of medicine the tradition is predominantly British, as is the rest of life and thought of Australia. The new strains of Polish, Italian, Dutch and Yugoslav, which have been introduced into Australia since the Second World War, besides bringing a welcome variety and improvement in Australian cooking, are introducing

cosmopolitan thinking into the Commonwealth. The influence of the British tradition in medicine is seen in the ready acceptance of the closed hospital system as it exists in Britain. This in large measure excludes the general practitioner from practice in hospital, and the consultant in both medicine and surgery, who has long been familiar with the honorary system as seen in Britain, accepts it as a natural development in the Australian hospital system. Most of the consultants are Members or Fellows of the British Royal Colleges, or hold degrees from the Royal Australasian Colleges. Postgraduate degrees are possessed very frequently by the general practitioners also. The Australian has learned to "honour the physician" and, by and large, the profession ranks high in the community.

In 1901 the Federal form of government was established with a written Constitution. Under this Constitution residual power remains with the State,

and health is a state responsibility.

Two types of hospitals exist in Australia, Firstly, there is the private hospital which receives a subsidy from public funds, but basically relies upon patient payments for its income. The larger private hospitals are run by religious organizations such as the Roman Catholic Church, the Methodist Church and the Church of England. Many of the larger private hospitals, such as the Mater Hospital in Brisbane, are well designed and well equipped. Smaller private hospitals are owned and operated by doctors or nurses and do not afford the same facilities of specialized care or diagnostic services as are to be found in the public hospitals. The beds in these private hospitals are available to all doctors in the community and physicians may admit and treat their patients in these hospitals without the supervision of an organized medical staff. This is a cause for real concern in the smaller hospitals and there is considerable interest in Canadian methods of the self-discipline of medical staffs and accreditation of hospitals.

The public hospitals are largely subsidized by the State. The revenue from the patients accounts for approximately one-half of the receipts of this type of hospital. The budget control is in the hands of State Hospital Commissions which have been known to change their political complexion with each change of government. The possibilities in this situation for interference by an outside authority through financial control are self-evident and often visible. Where State finances are adequate and the budgets not cut by all-powerful Boards, hospitals are found to be well equipped and the services

The staffing of these public hospitals is by honorary consultants who provide their services gratuitously in most instances. In Queensland, however, the honorary staff is paid by the hospital on

<sup>\*</sup>Presented at the 94th Annual Meeting of the C.M.A., Montreal, June 1961.

a sessional or half-day basis. The intern and resident staff is paid on a salary basis. In these public hospitals all the public beds are free. More than half of all hospital beds in Australia are so-called public beds, and the medical services to the patients in these public beds are rendered by the honorary consultants without cost to the patient. In this way, the honorary system substantially reduces the cost of medical services and indirectly subsidizes medical benefit insurance plans.

The only compensation the honorary consultant has in some of the public hospitals is that certain beds are designated as "intermediate beds" and he is privileged to admit his patients to these beds. The patient is privileged also to pay for his physician's services and has the rights of a private patient. However, the number of "intermediate beds" is small in proportion to the number of public beds. There has been considerable agitation on the part of the profession to have more beds designated "intermediate", but the Hospital Commissions are not anxious to have this happen, as it has, naturally, certain political possibilities and elections can be won or lost on issues such as this in many of the States. Government can be benign, but politics can be malignant, In Northern Tasmania a hospital is being built in two sections, 10 miles apart, to satisfy the demands of two political districts. The staff is transported by bus between these two parts of the same hospital. In Queensland all public beds are free. In other States admission to public beds is usually by a means test. This has possibilities for manipulation, especially in rural areas. In smaller hospitals away from larger centres, specialist services are not always available, and the general practitioners in these instances assume the role and function of honoraries. The number of doctors and their appointments is determined by the State Hospital Commission. This has great possibilities for weal or woe depending on the calibre of the members of the Hospital Commission.

The Hospital Commissions favour filling of all hospital posts by full-time salaried physicians. This has occurred in at least one area in New South Wales. Pathologists and radiologists are full-time salaried employees of the hospitals, and surgeons and others who offer special technical skills are likely to become full-time salaried physicians also.

Approximately 60% of the medical profession of Australia are general practitioners. They are well trained and without exception are very busy. The individual physician often practises from his own home, but there is a growing tendency to have separate offices. This almost becomes imperative when a man sees sometimes 80 to 90 patients a day. The average would be nearer 40 to 50 patients treated a day, and very few of these patients are seen in hospital, because the general practitioner has little access to hospital except in the peripheral areas. The general practitioner is the mainstay of group practice which is developing in the suburban

sections of the big cities. These groups usually consist of three, four or even more general practitioners and one or two consultants. These consultants practise in the periphery and have in addition offices, or office space, on the "Harley Streets" of the big cities, such as McQuarry Street in Sydney. There does not seem to be any scarcity of medical men, and one wonders if the load on the general practitioner is the result of a fee-for-service medical economy. Certainly the Australians do not appear to be neurotics or perhaps they have the attitude "Why worry? The Government or the PLAN pays the bill!" The general practitioner financially is satisfactorily rewarded and is generally content with the arrangement under which he works, so content that he often does not want to accept appointments on hospital services which might mean less time in his office.

The young specialist consultant, well trained and eager to put to use his training, finds it hard to break into the honorary system and often experiences many lean years, unless he has some special access to the inner circle.

Health insurance in Australia became a major interest of Government as early as 1938, but the Second World War intervened and no direct move was made in this field until 1944, when the Pharmaceutical Benefits Act was introduced and passed the same year. This Act imposed so many restrictions on the profession that the Victoria Branch of the B.M.A. was aroused and appealed to the High Court of Australia, which declared the Act ultra vires. In 1946 the Chifley Government obtained the consent of the electorate to permit the Commonwealth Government to act in: "the provision of maternity allowances, widow's pensions, child endowments, unemployment, pharmaceutical, sickness and hospital benefits, medical and dental services (but not so as to authorize any form of civil conscription), benefits to students and family allowances."

On the strength of this referendum a second Pharmaceutical Benefits Act was introduced and passed in 1948. Again this was unacceptable to the profession because of restriction to a limited government formulary with severe penalty clauses. The medical profession refused to use the government prescription forms and would not accept limitation to the government formulary. This Pharmaceutical Benefits Act, the second one, was amended in 1949 to prohibit physicians from prescribing any drug listed in the government formulary other than on government prescription forms. This amendment was declared ultra vires, as the court ruled that the coercion involved in its enactment entailed civil conscription. In the General Election which followed, the Labour Party was defeated and thus ended the "Battle of the Bottle".

The new coalition government had as its Minister of Health, Sir Earl Page. Sir Earl introduced the system of Commonwealth Benefits, which appealed to the self-reliance and individualism of the

Australian people, because through these benefits the Government offered to help those who, through participation in an insurance arrangement, had undertaken to help themselves.

Medical benefits prior to 1949, as mentioned before, had been supplied usually by a Friendly Society. This was medical care on a contract basis, and in 1949 the B.M.A. Australia announced that it considered contract practice to be unethical. The medical profession this same year organized Benefit Societies to provide medical pre-payment for the general public. These societies were set up as non-profit plans, with members of the profession and prominent lay members of the community giving their services as board and committee members without remuneration.

Sir Ronald Grieve, Chairman of the Medical Benefits Association of Australia, was interviewed by one of the members of the delegation that recently visited Australia from the C.M.A. Sir Ronald was asked, "What principles do you consider essential in setting up a workable Health Insurance Scheme which might be taken as the basis of a national scheme?" He replied, "In the first place, it should be voluntary and non-profit. In the second place, the government should subsidize the benefits provided for the voluntary organizations, to keep it within the contributor's means. In the third place, voluntary organizations should be directed jointly by both medical representatives and lay representatives of contributors. In the fourth place, the only government control should be that of audit and the safeguarding of the contributors' moneys. Fifthly, it is essential in preserving the stability and solvency of insurance funds that the contributor should pay a fraction of the doctor's fee; in other words that the benefits should fall short of the fee by amounts sufficient to ensure that neither contributor nor doctor will owe the service, Sixthly, it should be fully comprehensive; that is, it should cover all types of medical service. And in the seventh place, there must be a waiting period of say 2-3 months between joining the insurance fund and the rights to benefits, in order that the incentive to insure will be constantly present."

Sir Ronald was asked, "Do you find that you get sufficient coverage of the population of Australia with a scheme embodying these principles?" He replied, "To start with, 10% of the population is covered by free pensioner and medical service, armed services and repatriation medical schemes, free service to members of religious orders, etc. This means that 90% of the population is insurable. It is a fact that 85% of this 90% are already insured." He was asked, "Do you find that abuse is minimized by the payment of a portion of the doctor's bill by the patient?" He stated, "We regard this as vital. Under the Australian National Health Act no insurance fund is permitted to pay in combined Government and Fund Benefit more than 90% of the doctor's account. The patient is encouraged administratively to pay the doctor's bill and then receive reimbursement. But in cases of established hardship the amount of the combined benefit may be paid to the contributor in the form of a cheque payable only to the doctor rendering the service." A further question was asked, "Do you find that this type of scheme is economical to Government?" Sir Ronald replied, "Beyond a doubt. This scheme costs the Government nothing for administration except that of audit and supervision; the Fund pays the whole cost of administration. For this reason, and for the reasons which I have indicated as preventing abuse, the cost to Government of this scheme could never attain the uncontrollable dimensions of, for example, the British scheme." The final question asked was, "Is there any other factor which you regard as essential for the success of such a scheme?" "Yes," he replied, "First there must be administrators of top-grade quality. Secondly, as the very motive of such a scheme is the appeal to the self-reliance of the average person in a democracy, there should at all times be the closest contact with, and mutual confidence between, the leaders of the government and the leaders of the insurance fund.

Registered organizations generally reimburse their members by cash payments. The contributor obtains medical attention from the doctor of his choice and pays the doctor's account. He then claims from the organization payment of the Commonwealth and Insurance Fund Benefits to which he is entitled.

The benefit paid by any Fund for a particular service must at least match that which the Commonwealth has agreed to pay, as listed in the schedule of the National Health Act. This is a very comprehensive schedule covering a multitude of medical, surgical and diagnostic procedures. For an office and home consultation these combined benefits range from 12s. to 16s, (\$1.38-\$1.84 approx.); for obstetrics £8.5.0. (\$19.15) to £12.0.0. (\$27.85) Australian; for major operations £33.15.0. (\$78.30) to £60.0.0. (\$139.20). The amount of reimbursement varies because the Fund benefits vary depending on the rate of premium paid, but the Commonwealth benefit is constant. These two benefits combined represent usually about 65% of the total bill. The weekly cost of medical benefits ranges from 1/3 to 2/- (14c to 23c) for a single person; 2/6 to 4/- (28c to 46c) for families. The general principles enunciated by Sir Ronald Grieve in the interview described are in large measure applied to all the medical benefit schemes approved by the Commonwealth.

To provide for those over 65 and to take care of pre-existing ailments, chronic illness and those who have exceeded the maximum fund benefits, Special Accounts have been set up by all the major medical benefit societies. If at the end of a financial year the payments made from these special accounts for benefits to contributors and for reasonable management expenses, exceed the contributions credited to the account, the amount of the deficit is reimbursed by the Commonwealth. In short the Commonwealth guarantees the special accounts. All other members of the contributor's family must be placed in the special account as well, together with the premium paid on their behalf. The contributor placed in a special account must remain there for a period of at least two years.

In the year which ended April 30, 1960, 72% of the population was covered by these Medical Benefits Plans, at a cost to the Commonwealth of some £91/4 million. The Australian public seems to be well satisfied. If in-hospital fees are too high the patient can often elect to go into a public bed and thus incur no expense. No fee schedules are published, but in spite of this there is no exploitation to any extent through excessive extra billing. Any deterrent feature which might work to keep the patient away from the physician does not seem evident, as the Pensioners' and Special Funds take care of any who might be deterred. There does

not seem to be any delay in diagnosis. There is a certain degree of inflexibility in the Benefits Scheme, because the Commonwealth benefit has been relatively fixed since 1951. It has been

difficult for doctors to increase their fees, even though the country has experienced a substantial degree of inflation. The general practitioners like the plan on the whole, as they are paid for all services which they give and are certain to have few or no bad debts. The consultants, on the other hand, feel that they are subsidizing the scheme by the amount of their free hospital work and they feel that their fees are being dictated to the pro-

Fund benefit fee allowed.

The present Government, while recognizing there are some defects in this method of meeting health needs, are quite pleased with it. Increasing cost is accepted, and the feeling at Canberra is that abuse of the Health Scheme is minimal. The costs of administration are kept extremely low, as all the disbursements are made through the Benefits Plans.

fession by the total of the Commonwealth plus the

The Hospital Benefits Scheme, along the same lines as the Medical Benefits Scheme, was initiated in 1952 and a subsidy of 4/- a day was paid by the Commonwealth Government to hospitalized patients who already had some form of voluntary insurance against the cost of hospitalization. This 4/- per day was in addition to the 8/- per day which had been paid for some five years by the Commonwealth Government in respect of all citizens in hospital, whether insured or not. Once again the higher the premium paid by the individual to his insurance plan the higher the Hospital Benefit, and the higher the additional Commonwealth Benefit. As in the case of Medical Benefits, the Commonwealth guarantees the Special Accounts for pre-existing conditions and chronic illness.

The Pensioners' Medical Service, introduced in 1951, was a very real adjunct to the Medical Benefits Scheme. This is a means of providing free gen-

eral practitioner medical attention to all eligible pensioners and their dependants who qualify on a means-test basis. The profession accepts a direct payment from the government department at a sessional rate of approximately 50% of their usual fees. There is no provision for in-hospital services, as it is expected that the recipients of Pensioners' Medical Service will occupy a public bed. The doctors in this service are paid mileage charges in excess of two miles in the country and three miles in the city. In 1959-60 there were 740,000 pensioners and dependants enrolled and these were taken care of by 5685 participating doctors at a cost to the Commonwealth of £4,100,000.

The interesting thing about this Service is the special boards of enquiry composed of members of the profession, which are set up to watch any possible abuse of the Plan. The cases that these boards have had to deal with have been few and the disciplinary actions, including temporary loss

of licence, have usually been severe.

Pharmaceutical Benefits, that initial battleground in the "Battle of the Bottle", was again tackled by Sir Earl Page in 1950 and a new program introduced, which provided for all patients free of charge costly "life-saving and disease-preventing drugs". Costs increased alarmingly from £7,600,000 in 1952 to £20,700,000 in 1959. In March 1960 5/- per prescription was imposed except for pensioners. Public reaction to the 5/- surcharge was mixed. Some resented it, others considered it a reasonable amount to pay for a prescription which would otherwise cost from £5 to £10. The profession on the whole is not happy with the scheme for pharmaceutical benefits.

Many people have felt that Medical Benefits as seen in Australia could be readily transplanted to Canadian soil. The closer one looks at the Australian scheme, the more one feels that this is not feasible. However, there are certain features of the scheme, such as patient participation, the close relationship with government, the definite interest of the profession in the insurance plans and the careful discipline which eliminates any abuses-all these could be readily accepted and might be very useful in any comprehensive plan

for health insurance in Canada,

422 London St. Sherbrooke, P.Q.

#### PAGES OUT OF THE PAST: FROM THE **JOURNAL OF FIFTY YEARS AGO** GALLBLADDER CARCINOMA

It is in this class of cases, in which the gall-bladder is contracted down upon a mass of stones, that secondary carcinoma is likely to develop. In our experience 2.25 per cent. of all operations upon the gall-bladder and biliary tract have shown malignant complications. The danger of carcinoma alone is five times as great as the mortality following operations for the relief of simple gall-stone disease.—William Mayo (Rochester, Minn.), Canad. M. A. J., 1: 866, 1911.

#### CASE REPORTS

#### PAPILLARY CARCINOMA ARISING IN A THYROGLOSSAL TRACT\*

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Carcinomatous degeneration of ectopic thyroid tissue in a persistent thyroglossal tract represents a rare complication of a relatively common anomaly. This complication has been documented on six previous occasions.<sup>1-5</sup>

A 73-year-old white male entered the Mount Auburn Hospital, Cambridge, Mass., in coma with left-sided facial and body paresis, a history of hypertension for many years and an earlier attack of right-sided paresis from which he had recovered. On physical examination the patient was deeply comatose with left-sided spastic paralysis. No masses were found in the neck. The hospital course was marked by deepening coma and progressive respiratory distress, culminating in death four days after admission.

The major gross autopsy findings were recent thrombosis of the right middle cerebral artery, massive infarction of the right cerebral hemisphere, a healing infarct of the left internal capsule and multiple pulmonary emboli. A cystic mass was found in the midline of the neck, midway between the hyoid bone and the thyroid cartilage, attached to the platysmus muscle and to the cervical fascia. The cyst was tense, and so tightly bound to the deep dermis and fascia that no plane of dissection was found. Because of this, a layer of fibrous tissue was removed with the cyst, and a thin cord-like structure anchoring the cyst to the hyoid bone was severed. There was no demonstrable connection between the cyst and the thyroid gland. After formalin fixation, the cyst measured 2.6 x 2.1 cm. and on sectioning contained turbid yellow fluid. The internal diameter was 1 cm. and the inner lining was smooth. The cyst wall was firm, thick, grey-white, opaque and non-calcified, and blended into the adjacent fatty fibrous tissue. The thyroid gland weighed 21 g., was bilobate, and on serial sectioning had a uniform reddish-tan parenchyma. No nodules, areas of fibrosis, or calcification were present in the thyroid gland. The cervical lymph nodes were unremarkable.

Microscopic examination of the organs confirmed the major gross findings. The cystic structure from the neck was lined in part by a single flattened layer of nonciliated columnar cells, and in part by a layer of inflammatory exudate, consisting of lymphocytes, foamy histiocytes admixed with strands of fibrin, occasional hemosiderin-laden histiocytes, and moderate numbers of fibroblasts. The wall of the cyst was composed of thick acellular hyalinized connective tissue. The lumen contained strands of fibrin and proteinaceous material in which were scattered foamy histiocytes (Fig. 1). Fibro-fatty tissue abutted on two-thirds of the external surface of the cyst, and a nodule of thyroid tissue and papillary tumour covered the remainder. The



Fig. 1.—A portion of the thyroglossal cyst showing exudate in the lumen and thyroid follicles abutting on the outer wall of the cyst.

nodule of thyroid tissue, which was in part neoplastic, was not encapsulated and was composed of both follicular and papillary elements. The follicles in the non-neoplastic tissue were of medium size, filled with pale-staining colloid and lined by flattened cuboidal cells. These elements were in juxtaposition to the cyst wall. The tumour had a papillary pattern with cystic spaces, devoid of colloid, partially or completely filled by papillary infoldings of the epithelial lining. The lining cells of the papillary processes were plump and cuboidal, with clear cytoplasm and large moderately hyperchromatic nuclei which varied slightly in size (Fig. 2). Some papillary processes were calcified. A



Fig. 2.—An area of papillary carcinoma with dense stroma.

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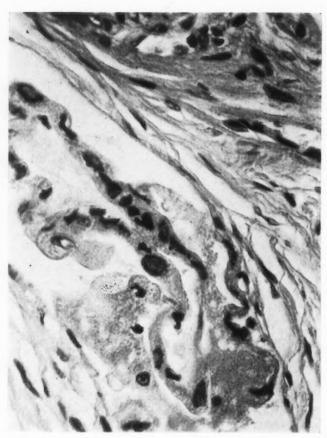


Fig. 3.—A papillary process projecting into the lumen of a lymphatic. Note variation in size of the nuclei.

dense hyalinized stroma was present, whereas in the follicular area the stroma was loose. Masses of tumour cells were found in one small lymphatic channel, and a papillary process composed of tumour cells, coated with fibrin, projected into the lumen of a medium-sized lymphatic (Fig. 3). Sections of the thyroid gland revealed a normal follicular pattern.

#### DISCUSSION

The true incidence of persistent thyroglossal tract is unknown, partly because it may be asymptomatic. However, the persistent thyroglossal tract gives rise to complications so frequently that it is generally included in the differential diagnosis of midline or cervical sublingual masses. Major complications are cyst formation, abscess or fistula. The question of lingual thyroid is considered separately.

The fact that thyroid tissue may be present in or adjacent to a persistent thyroglossal tract is well known, but the frequency is not well documented. Incidence varies from 1.7% to 7.6% with a mean of 5%. The relatively low incidence of ectopic thyroid tissue in the thyroglossal tract and the fact that surgical excision is performed for the complicated cases, usually in children and young adults, provide partial explanations for the rarity of carcinomatous degeneration.

Keeling and Ochsner,<sup>4</sup> in 1959, reviewed the five cases published in the medical literature up to that time and added two of their own. The first patient in their series had a carcinoma arising

in a lingual thyroid. Objection to inclusion of Case 2 in that series may be made because during the primary excision of the cyst no tumour was found, but at re-operation five months later, two nodules of papillary carcinoma were found attached to the tracheal rings. It might be argued that the tumour found at the second operation represented metastases from a primary tumour in the thyroid. The thyroid was not examined microscopically, and it is well known that occult sclerosing papillary carcinomas of the thyroid of almost microscopic dimensions may give rise to metastatic nodules.

Ghent and Waugh,5 in a recent case report, combined some of the cases of carcinoma arising in lingual thyroid glands with the series of Keeling and Ochsner. They titled their series "Carcinoma in Thyroglossal Duct Remnants". A lingual thyroid may represent a persistent remnant of the thyroglossal tract, or it may represent the entire tract. Montgomery,7 in a review of 144 cases of lingual thyroid, estimated that in two-thirds of the cases the lingual thyroid represented the only thyroid tissue present. This was verified in 29 cases by the development of myxedema following surgical removal of the lingual thyroid. If a lingual thyroid represents the only thyroid tissue in the body, it should be classified as ectopic thyroid tissue and not as a remnant of the thyroglossal tract. For the same reason, the normal cervical thyroid is not called a remnant of the thyroglossal tract, although in fact it represents the only remnant of the tract in the majority of people. Therefore carcinomas arising in lingual thyroids should be recorded separately from those arising in persistent thyroglossal tracts.

In all of the reported cases of carcinoma arising in a thyroglossal tract, the tumour had its origin in ectopic thyroid tissue in or bordering the cyst wall. No report was found in which the carcinoma could be traced to the epithelial lining of the thyroglossal tract. The authors of previous case reports have not commented on this aspect. The tract may be lined by columnar or squamous epithelium, and in theory could give rise to a squamous or a glandular carcinoma. If carcinomatous change occurs in the lining of the tract, it might provide an explanation for the occasional case of so-called metastatic carcinoma in cervical tissues that is usually attributed to a hidden primary in the nose or throat. Clute and Smith<sup>8</sup> alluded to this possibility in explaining squamous cell carcinoma of the thyroid, although there was no evidence of a persistent tract in their case.

Of the carcinomas originating in ectopic thyroid in thyroglossal tracts, four were in females and three in males. Two occurred in children, and one of these is the only case in which metastasis occurred. The case reported here is the only one in which diagnosis was made at autopsy, the remainder having been discovered during surgical treatment. Five of the seven tumours reported were papillary and two were follicular carcinomata.

#### SUMMARY

A seventh case of carcinoma arising in ectopic thyroid tissue in a persistent thyroglossal tract is presented. Reasons are advanced to account for the rarity of the condition and for recording these cases separately from carcinomas arising in lingual thyroids. Persistent symptomatic thyroglossal tracts should be surgically removed to prevent this rare complication.

#### REFERENCES

- CLUTE, H. M. AND CATTELL, R. B.: Ann. Surg., 92: 57, 1930.
- ARONOFF, B. L.: Am. Surgeon, 18: 362, 1952. O'KANE, C. R. AND STRAUS, F. H.: Ann. Surg., 138: 805, 1953.
- 1953.

  4. KEELING, J. H. AND OCHSNER, A.: Cancer, 12: 596, 1959.

  5. GHENT, W. R. AND WAUGH, D.: Canad. J. Surg., 4: 79, 1960.

  6. WARD, G. E., HENDRICK, J. W. AND CHAMBERS, R. G.: Surg. Gynec. & Obst., 39: 727, 1949.

  7. MONTGOMERY, M. L.: West. J. Surg., 44: 122, 1936.

  8. CLUTE, H. M. AND SMITH, L. W.: Arch. Surg., 18: 1, 1929.

#### RETROPERITONEAL FIBROSIS

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The recognition of retroperitoneal fibrosis as an entity dates back to 1948 when Ormond<sup>1</sup> described two patients with a chronic inflammatory, fibrotic lesion in the retroperitoneal area. Since this time, more than 40 such cases have been described in the literature. The nomenclature has been somewhat confused because various authors have emphasized different features of the lesion; terms such as periureteral fibrosis, perirenal fasciitis, periureteral fasciitis, retroperitoneal inflammation and periureteritis obliterans have been proposed. The typical appearance and location of the process is of a dense fibrous mass up to 2 cm. thick lying immediately anterior to the bodies of the lumbar vertebrae and the fascia covering the iliopsoas muscles, extending from the level of the kidneys, above, to that of the bifurcation of the common iliac arteries, below, and bound laterally by a line about 1 cm, lateral to the ureters on each side. and fading out over the brim of the pelvis. In its fully developed form, the lesion may extend to the crura of the diaphragm and surround the hilus of each kidney. Less extensive masses may be found in any localized region within these boundaries and the condition may be unilateral. In one case, it was observed to penetrate the diaphragm and involve the pericardium.2 The process envelops and progressively constricts some or all of the structures in the same site of involvement.

The present report describes an interesting case in which retroperitoneal fibrosis may be assumed to have been present at least ten years before death.

#### CLINICAL HISTORY

The patient was first admitted to this hospital in 1950 at the age of 60 years, with bronchopneumonia and the complaint of chronic fatigue of six months' duration. Laboratory investigation showed the following: 3+ albuminuria with a few red and a few white cells in the urine, erythrocyte sedimentation rate of 120 mm. in 1 hour, hemoglobin concentration of 64% or 10 g. per 100 ml., white blood cell count of 16,900

per c.mm., blood pressure of 140/84 mm. of Hg, and a non-protein nitrogen content of the blood (N.P.N.) of 64 mg. per 100 ml. Slight benign prostatic hypertrophy was found on physical examination but it was noted that the N.P.N. was unusually high for the degree of prostatic hypertrophy noted. While in hospital the patient developed a urinary tract infection due to Pr. vulgaris, and in spite of therapy, this infection progressed to pyelonephritis and the N.P.N. determination rose to 78 mg. per 100 ml. An intravenous pyelogram showed a right-sided hydronephrosis and the left kidney did not excrete dye. After having been elevated to over 100 mg. per 100 ml., the N.P.N. fell gradually to 54 mg. per 100 ml.; the residual bladder urine was less than half an ounce. After two months in hospital, the patient was discharged with the final diagnosis of benign hypertrophy of prostate, left bronchopneumonia, right hydronephrosis, and a non-functioning left kidney. He returned home but was able to work only half-days because of fatigue. In 1951, more than a year later, he was readmitted for investigation of frank hematuria which occurred on three occasions; he complained of a constant nagging pain in the right loin which was relieved by the passage of blood.

On examination, there was marked tenderness in both costovertebral angles. The blood pressure was 160 /80 mm. of Hg. The N.P.N. was 50 mg. per 100 ml. and the urine showed a trace of albumin. Cystoscopy showed no abnormality but there were 40-50 white blood cells per high-power field in the urine from the left ureter. There was also evidence of prostatic hypertrophy. The retrograde pyelogram was interpreted as showing bilateral hydroureters in the upper thirds, with a gradual concentric tapered narrowing. The region of maximum narrowing began at the level of the fourth lumbar vertebra just below a sharp medial angulation of the ureters and extended to the pelvic brim. The involved segments were displaced toward the midline (Fig. 1). However, the significance of these x-ray findings was not appreciated at the time. The patient was followed at intervals of a few months in the outpatient department where it was found that the N.P.N. remained at about 50 mg. per 100 ml.; he was told that he had "Bright's disease".

In 1956, he was admitted for treatment of hypertensive heart disease, congestive heart failure and a cerebrovascular accident. The blood pressure was now 200/108 mm. of Hg and the N.P.N. was 80 mg. per 100 ml. In 1957, he experienced intermittent claudication for the first time.

The final admission in February 1960 was required for treatment of a chronic ulcer which had progressed to gangrene of the left foot. Treatment of this ultimately

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Fig. 1.—This retrograde pyelogram was made in 1951. Note the bilateral hydroureters in the upper thirds with a gradual concentric tapered narrowing becoming maximal at the level of the fourth lumbar vertebra. The narrowed segments of the ureters are displaced toward the midline. (Retouched.)

required amputation of the left leg. The blood pressure at this time was 180/80 mm. of Hg and the N.P.N. was 148 mg. per 100 ml. There was 3+ albuminuria, and culture of the urine grew mixed bacteria. With therapy, the N.P.N. was reduced to 60 mg. per 100 ml. However, in spite of continued therapy the urinary infection recurred and the N.P.N. rose to 183 mg. per 100 ml. The patient became drowsy and comatose and finally died two weeks after amputation of the leg.

#### AUTOPSY

#### Gross Findings

At the autopsy performed by Dr. V. B. Fowler, the heart weighed 510 g. and showed moderate left ventricular hypertrophy. There was a large recent infarct involving the anterior part of the septum and the adjacent part of the anterior wall of the left ventricle. The coronary arteries showed marked arteriosclerosis with severe calcification. The aorta showed severe arteriosclerosis and below the level of the renal arteries the intima was calcified, diffusely ulcerated and covered by a mural thrombus.

The right kidney weighed 100 g. and the left kidney 60 g. The renal capsules were thickened, and were stripped off with slight difficulty to reveal irregularly scarred cortical surfaces. There was marked bilateral hydronephrosis which had resulted in severe compression and atrophy of the left kidney and less marked atrophy of the right kidney. Each of the enlarged renal pelves contained clear brown urine. The renal vessels were patent.

A flattened mass of firm, pale grey tissue measuring about 2 cm. in thickness was present in the retroperitoneal space surrounding both ureters in their

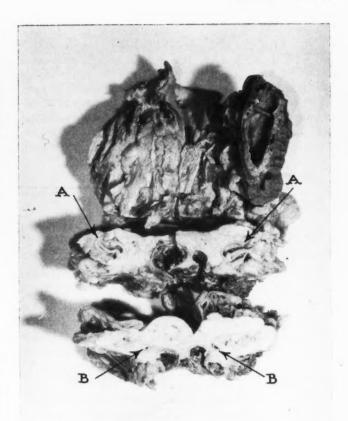


Fig. 2.—The retroperitoneal mass after fixation, from the posterior aspect. Slices from the mid-portion and the lower quarter have been turned on edge to show the fibrous tissue surrounding the aorta, inferior vena cava and ureters. At A (above) the ureters are dilated, and at B, the ureters are constricted. Note the widely dilated renal pelvis on the right.

middle thirds and extending around the aorta and inferior vena cava at the same level. The process was slightly more extensive on the left side and extended to the lower margin of the fifth lumbar vertebra in the midline; laterally, the process extended to about 1 cm. lateral to the ureters and continued along the common iliac arteries to fade out at their bifurcations. The ureters were obviously narrowed by the sclerosing process but a probe could be passed through their length without difficulty (Fig. 2).

Neither the kidneys nor the renal pelves were involved by the fibrous tissue, but there was a separate

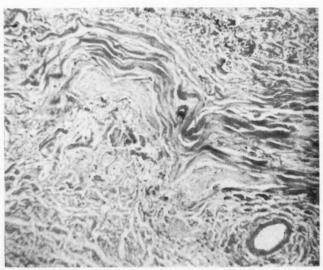


Fig. 3.—Photomicrograph of a section of the retroperitoneal mass, showing wavy bands of moderately dense collagenous connective tissue.

mass of similar, firm, pale grey, fibrous tissue measuring about 1.5 cm. in diameter at the hilus of the spleen. The splenic vein at the site was involved by an old thrombotic, recanalized occlusion.

#### Microscopic Description

Microscopically, the retroperitoneal mass was composed of wavy bands of moderately dense, irregularly arranged, collagenous connective tissue. Relatively few fibroblasts were present between the prominent, wide, collagen fibres and there was a very sparse, lymphocytic infiltration (Fig. 3). Many small blood vessels and nerves were embedded in the connective tissue but, although the ureters were surrounded by similar tissue, they were separated from it by a thin but definite layer of loose areolar tissue. The walls of the ureters were infiltrated by lymphocytes and plasma cells but the mucosa was intact. The nodule from the hilus of the spleen was similar to the main mass in microscopic appearance.

Multiple sections of abdominal lymph nodes failed to reveal any evidence of primary lymphoma or metastatic carcinoma. Sections of the kidneys showed evidence of severe chronic pyelonephritis.

#### DISCUSSION

Dineen, Asch and Pearce,2 in one of the recent reviews of the literature on this subject, reported that the ages of the patients with retroperitoneal fibrosis ranged from 23 to 69 years with an average of 44 years. They noted that 69% of the cases occurred between the ages of 40 and 60 years and about 79% of the patients have been males. The signs and symptoms depend on whether the fibrosis first stiffens the lumbar spine, reduces blood supply to lower limbs, embarrasses venous return, or causes hydronephrosis, either by constriction or by the prevention of peristalsis in the ureters. Therefore, the patient may complain of backache, intermittent claudication, swelling of both lower limbs, anuria, oliguria, anorexia, nausea, vomiting, vague abdominal pain, weight loss, flank pain or limitation in flexion of the lumbar spine.

Idiopathic retroperitoneal fibrosis must be distinguished from retroperitoneal fibrosis due to regional ileitis, ulcerative colitis, diverticulitis, and appendiceal abscesses. These primary sources of inflammation may be diagnosed by means of suitable clinical and pathological study. The condition called periureteritis plastica3 is probably a rarer and separate disease involving only the ureters and characterized by a peculiar, marked, 1-2 cm. thick hyperplasia of the loose areolar tissue surrounding the ureter and giving rise to the so-called garden hose appearance.

Several theories concerning the etiology of idopathic retroperitoneal fibrosis have been proposed. In biopsies of some cases there is a resemblance to Weber-Christian's disease, or non-suppurative panniculitis.<sup>2</sup> Possibly the condition begins in this manner and later progresses as the fibrous tissue accumulates. It has been suggested that the condition may result from organization of fibrin after bleeding due to trauma or after exudation associated with inflammation.4 Not all cases have a history of trauma or inflammation but the condition may be quite slow to develop. It has been reported to occur after extrayasation of contrast material during retrograde pyelography.<sup>5</sup>

The structures involved by this process are said to be in a common fascial compartment (Gerota's fascia) but this space appears to be poorly defined and there is some debate as to whether it is separated by a midline partition. In any event, the condition is not always confined to these limits.2,7 The histological resemblance of this condition to keloid has been noted.1,4 The treatment of choice is ureterolysis, or surgical freeing of the ureters from the fibrous tissue mass, and patients treated in this way have done very well. Radiation to the mass has been followed by improvement in some cases but has failed to help others.2, 4

#### SUMMARY

A case of retroperitoneal fibrosis which had been present for at least ten years before death has been presented. The distribution of the main lesion was typical of that previously described for this condition but an additional smaller mass of fibrous tissue identical in microscopic appearance to the main mass was present at the hilus of the spleen.

I wish to thank Dr. A. J. Blanchard for his assistance in the preparation of this report, and the Medical Art and Photography Department of Sunnybrook Hospital for the preparation of the photographs.

#### REFERENCES

- ORMOND, J. K.: J. Urol., 59: 1072, 1948.
   DINEEN, J., ASCH, T. AND PEARCE, J. M.: Radiology, 75: 380, 1960.
   HEJTMANCIK, J. H. AND MAGID, M. A.: J. Urol., 76: 57, 1956.
   HANGERT D.: Duit J. Surge, 46: 2, 46: 2.

- 1956. 4. HACKETT, E.: Brit. J. Surg., 46: 3, 1958. 5. LANDES, R. R. AND HOOKER, J. W.: J. Urol., 68: 403, 1952. 6. HUTCH, J. A., ATKINSON, R. C. AND LOQUVAM, G. S.: Ibid., 81: 76, 1959. 7. RAPER, F. P.: Brit. J. Urol., 28: 436, 1956.

#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

It has been said that the work of a school medical officer is in danger of becoming monotonous. Surely no work which opens so many doors is monotonous. The report of the superintendent of education of the province of Nova Scotia opens one-the campaign against ophthalmia neonatorum. The report of the school commissioners of the city of Halifax opens another-the fight against tuberculosis and all that the school can do to win the victory. The Act passed in Ontario opens a great door-the work for children who cannot compete with the others-that is, the ones who, if we do not take hold of them now, and make them selfsupporting, will make us support them and their children later on, in the most expensive of modern institutions-the hospitals, the prisons, the asylums, the poor-houses-as chronic invalids, blind, deaf, paupers, feeble-minded, insane, and criminals.-Canad. M. A. J., 1: 901, 1911.

#### THE CANADIAN MEDICAL ASSOCIATION

# JOURNAL DE

#### L'ASSOCIATION MÉDICALE CANADIENNE

published weekly by

THE CANADIAN MEDICAL ASSOCIATION

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### MORE ABOUT THE PREVALENCE OF ARTHRITIS

N A previous editorial in this journal (Canad. M. A. J., 83: 170, 1960) it was observed that "reliable prevalence estimates for rheumatoid arthritis, and comparability of statistics from different geographic areas require greater accuracy and uniformity of diagnostic criteria and more efficient and valid survey techniques than are presently available. Gradients of disease severity must be clearly defined. The degree to which mild or doubtful cases are included radically alters any prevalence figures, since such mild gradients of rheumatoid arthritis predominate, and cases of easily recognizable, classical disease are in the minority." The development of facilities and personnel for field studies of the epidemiological aspects of rheumatic and other diseases was urged. The various means of obtaining data on the prevalence of rheumatic disease were summarized and it was anticipated that one might look forward to clarification of the diagnostic significance of radiographic changes and the further adaptation of serological tests for rheumatoid factor as an epidemiological technique.

Newer knowledge about the epidemiology of rheumatoid arthritis in Northern Europe is the subject of a recent report by Lawrence, Laine and de Graaff (*Proc. Roy. Soc. Med.*, 54: 454, 1961) which provides valuable clues both to the environmental and genetic factors involved. The diagnosis of rheumatoid arthritis in this study was based on the criteria defined by the American Rheumatism Association which take into consideration such manifestations of rheumatoid disease as morning stiffness, pain on joint movement, articular swelling or effusion, subcutaneous nodules, radiographic changes typical of rheumatoid arthritis, a positive sheep-cell agglutination test (SCAT), the presence of certain changes in the synovial fluid and the

findings on biopsy of nodules or of the synovial membrane. In these studies more reliance was placed on the radiological and serological findings because the application of the A.R.A. criteria is not entirely free from inaccuracies due to differences in observer interpretation.

The prevalence of rheumatoid arthritis was assessed clinically, radiologically and by means of the sheep-cell agglutination test (SCAT) )in seven population samples in the United Kingdom, Finland and the Netherlands. Two of these surveys included all persons over 15 years of age. In the remaining five population studies, complete radiological and serological data were available only on persons in the 55-64 year age group. The total number of persons in these samples was 4536 of whom 3999 were examined, a completion rate of 88%.

In the population samples from Leigh and Wenslevdale, two communities in the north of England in which all age groups from 15 onwards were included, 2.5% of males and 6.0% of females had definite or probable rheumatoid arthritis as defined by the A.R.A. criteria. Radiological evidence of erosive arthritis was encountered in the hands or feet in 3% of males and 3% of females but severe grades were more often encountered in the females. Radiological evidence of cervical rheumatoid arthritis was found in 5% of males and 5% of females. Other sites were much less frequently affected. The sheep-cell agglutination test (SCAT) was positive in 3.7% of males and 4.4% of females. The proportion of positive tests rose with age, reaching a maximum of 11% positive in males and 9% in females in the older age groups. Only a third of those with a positive SCAT had clinical or radiological evidence of rheumatoid arthritis.

Among other interesting observations that emerged from these surveys was the fact that the complaint threshold of individuals varied considerably in different areas and in different occupational groups in the same area. In Leigh, for example, rheumatic complaints were only half as frequent among miners' families as in the rest of the population, despite identical radiologic changes.

The radiological diagnosis of rheumatoid arthritis rests mainly on the recognition of erosions of bone, chiefly at the joint margins of the metacarpal and metatarsal heads. Cartilage erosion, osteoporosis and the formation of periosteal new bone are useful guides when interpreted by experienced personnel. In the cervical spine, ankylosis of the apophyseal joints with subluxation at the disc above or below the immobile joint is a significant sign of rheumatoid disease. These three sites, the metacarpo-phalangeal and metatarso-phalangeal joints, and the apophyseal joints of the cervical spine, should be examined radiographically as a routine procedure. It is of interest to note, by the way, that the standards for the radiological criteria of rheumatoid arthritis and other rheumatic diseases, as adopted after the Seventh International Congress on Rheumatic Diseases in Toronto in 1957, are now being made available in the form of an atlas.

Two types of serological tests have, in the main, been used in studies on rheumatoid arthritis: (1) the sheep-cell agglutination test (SCAT), which depends on the ability of certain rheumatoid sera to agglutinate sheep or human red cells sensitized by anti-sheep or anti-human erythrocyte rabbit serum, and (2) the latex fixation (LFT) or bentonite flocculation test (BFT), which depend on flocculation by certain rheumatoid sera of latex or bentonite particles coated with modified human gamma globulin. The SCAT is positive in some 70% of patients attending hospital in whom a diagnosis of rheumatoid arthritis has been confirmed, the LFT and BFT in 80%, Both the SCAT and BFT show an increasing titre with the age of the patients tested but neither shows a sex difference at any age group, the proportion of positive tests being essentially the same in males and females. The age distribution of positive tests in a mixed urban-rural population shows a stepwise increase between the ages of 15 and 74 with peaks every 20 years to a maximum of 11% positives in males and 9% in females in the older age groups. Individuals, as opposed to populations, do not have an increasing titre with age in these population samples, which suggests that the sheep-cell titre depends on past exposure to some antigen which has become less frequent over the past 70 years, so that the older members of the population stand a greater chance of acquiring a positive test. The relationship of the SCAT to the BFT is complex. Some common factor is shared by these tests but on the basis of present evidence that factor does not appear to be the presence of clinical rheumatoid arthritis. The association between rheumatoid arthritis and the serum tests is also obscure. Only one person in three with a positive SCAT, in two areas studied in this survey, had clinical or radiological evidence of rheumatoid arthritis. However, there is evidence that a positive SCAT predisposes to this disease in a quantitative way, for all those with a titre of 1 in 512 or greater had definite disease.

Information on geographic distribution is available mainly on the 55-64 year age group in Northern European countries. Definite rheumatoid arthritis, as defined by the A.R.A. criteria, showed much the same prevalence (between 2% and 3%) in all the surveys undertaken. The SCAT results showed a significant difference between urban populations (with 5% positive tests) and the rural areas (with 2-3% positive tests). Family studies indicated that in both seronegative and seropositive members of families of rheumatoid arthritis patients there is more clinical rheumatoid disease than in the population as a whole, but that only in seropositive relatives are there more radiological erosive changes. It is unlikely that environment, at least during adult life, is responsible for this familial aggregation but, if it is genetically determined, probably more than one locus is involved.

In random population samples, in addition to those who have obvious polyarthritis, there is a group of persons who give a history of previous polyarthritis but in whom all symptoms of the disease have completely subsided. Such "benign polyarthritis" was responsible for more frequent incapacity than was rheumatoid arthritis in Leigh, where 84 persons, 5% of the males and 7% of the females in that sample, had a history of past polyarthritis. Of these, four had mitral stenosis (although many more stated that their original illness was rheumatic fever), 15 had joint residua on clinical examination and only three had frank rheumatoid arthritis. Altogether 9% of the males and 10% of the females in this group had definite radiological changes in the cervical spine of the type usually associated with rheumatoid arthritis, compared with 3% and 4% respectively in the rest of the population. This condition of "benign polyarthritis" appears to be related more closely to rheumatoid arthritis than to rheumatic fever. The SCAT in persons with "benign polyarthritis", however, was positive in only 6% of males and 9% of females, little more than in the general population. All those in the Leigh sample with a past history of polyarthritis and a positive SCAT had clinical evidence of persistent rheumatoid arthritis (grades 1-4), and it may well be that the presence of a positive SCAT or some other predisposing factors such as psoriasis, for example, determines whether the arthritis in such cases clears after a time or persists.

Aside from the fact that recent investigations of this nature indicate that the actual prevalence of rheumatoid disease is appreciably greater than previously recognized, the broadening knowledge of the many faces of this disorder, as revealed by such epidemiological surveys of international scope, provides information of practical value to practising physicians. Application of this knowledge can contribute materially to the prevention of much unnecessary and avoidable disability among the millions of persons who suffer from this potentially. crippling ailment. The most effective use of appropriate forms of therapy depends upon an adequate understanding of the broad range of clinical manifestations with which rheumatoid arthritis may present, particularly in its milder forms and earlier stages.

### CONDITIONED REFLEXES AND PEPTIC ULCER

ONE of the striking features of Soviet medicine that impresses medical visitors to the U.S.S.R. is the amount of effort and enthusiasm that is devoted to the study of conditioned reflexes, and the importance attributed to this phenomenon in basic concepts of disease production. Some of our

scientists suggest that such studies of the role of the nervous system may not be receiving the attention that they merit in Western research. Others feel that the permeating influence of Pavlov on Russian medicine may have engendered unwarranted enthusiasm toward his concepts, and that the modern amplifications of his original ideas may not yield the rewards so confidently predicted by the votaries of his cult. Lack of intimate knowledge of the techniques and methodology employed by Soviet workers makes evaluation of these studies, and the conclusions drawn from them, very difficult, even for the Western reader who is fluent in Russian.

A comparatively simple study of this type, concerning the role of disturbances of corticovisceral interrelationships in the pathogenesis and course of peptic ulcer, has recently been reported by Shilov and Lebedev (Ter. Arkh., 4: 54, 1961). Although the functional disturbances in the stomach and the central nervous system, in the presence of peptic ulcer, are non-specific, and although investigations in this area have not produced any significant or useful results to date, it was considered that simultaneous studies of gastric and cortical functions might prove more rewarding. Such investigations were therefore carried out on 59 persons, 35 of whom had active duodenal ulcers; the remaining 24 were normal, healthy subjects. The secretory, motor, and acid-producing activity of the stomach was measured and correlated with the simplest type of conditioned reflex, that of blinking. After preliminary conditioning of the subject to the wink reflex, the duration of its latent period was measured at the mid-point of each 15minute interval while secretory and motility studies with a double-lumen gastric tube were being carried out. Gastric secretory activity was assessed by measurement of the volume of juice collected in a 15-minute period; acid production was measured as the absolute quantity of free hydrochloric acid in the same specimen of gastric juice; motor function was evaluated by recording the number of peristaltic waves, 5 cm. or more in amplitude, registered in a gastrogram over the same 15-minute period.

The average latent period for the conditioned reflex was interpreted as an index of "the functional status of the higher nervous system". Prolongation of this latent period was regarded as an indication of diminished stimulation and increased inhibition, while shortening of the latent period indicated the reverse.

Two types of reactions were observed. The first, or "normal", type showed no relationship between cortical function and gastric activity. In the second type there was either a "direct" or "reverse" relationship between the latent period of the conditioned blinking reflex and abnormalities of gastric function. In the former, prolongation of the latent period paralleled a decrease of secretion and acid

production, while shortening of the latent period was associated with intensification of these gastric functions. Gastric motor activity was usually changed in the direction opposite to secretory functions. In the second variant of this type of reaction, the gastric and cortical relationships were reversed.

Among healthy subjects the "normal" type of reaction predominated. This was particularly evident in the relationship between the latent period of the conditioned blinking reflex and the secretory function of the stomach. Of the 35 patients with pepticulcer, 30 showed abnormal correlation between gastric secretion and the reflex, while 20 showed an abnormal relation between hydrochloric acid production and the reflex. The correlation in the case of gastric motor function was abnormal in 18 of these subjects and normal in 17.

When the same studies were carried out 15 minutes after the introduction of 10 ml, of 10% sodium bromide into the stomach, the gastric secretory and acid-producing functions changed toward normal together with the conditioned reflex response. Similar but lesser improvement was noted in the case of gastric motor function.

It was also observed that bed rest, diet and appropriate drug therapy normalized these corticovisceral relationships in a number of patients with peptic ulcer. While such changes did not always parallel clinical improvement, the authors of this study expressed the view that these observations nevertheless emphasize the important role of nervous mechanisms, specifically those concerned with the "functional state of the cortico-visceral system", in the pathogenesis and clinical manifestations of peptic ulcer.

The difficulties inherent in such studies are stressed, even by the Russian workers. Anyone without intensive training in Pavlovian methods would face almost insurmountable difficulties in undertaking such research. It is of interest to recall that one of the reasons Pavlov gave for his refusal of an invitation to accept a post in Britain during the "twenties" was the lack of personnel in British laboratories trained in the techniques of conditioned reflex production.

It would appear unwise to reject categorically the findings of such studies of conditioned reflexes and their clinical significance. While one may doubt the wisdom of exaggerated absorption in this form of investigation to the exclusion of other approaches, it is possible that the conditioned reflex might provide an additional tool of value to research workers in the Western world. W.G.

#### Letter to the Journal

### BASIC ISSUES IN HOSPITAL AND MEDICAL CARE INSURANCE

To the Editor:

The article by Dr. J. Wendell Macleod (Canad. M. A. J., 84: 1434, 1961) is of great importance, and should be widely read and discussed. It represents the view of what I believe to be a minority group in Canadian medicine, but a minority which is intelligent and articulate and whose views on medico-political subjects are likely on these accounts to be given a disproportionate credence. It is not possible in anything short of an article of comparable length to give Dr. Macleod's views the line-by-line analysis which they deserve, but only to comment on some of his key statements.

Opportunity for good health has become a right, not a privilege", and "The right to health is an ethical stand." The phrase "a right to health" is becoming increasingly familiar as a part of the preamble to medico-political statements, and deserves a deeper analysis than it customarily gets. The definition of "right" occupies two closely printed whole-page columns in the Concise Oxford Dictionary, and of the numerous examples given perhaps "justification, fair claim, being entitled to" come closest to Dr. Macleod's meaning. With this definition, I do not think many would dispute the statement. Where many do disagree is with the coincident assumption that the only adequate provision of this right is by a universal, compulsory, government-controlled medical scheme, and that this socio-political method is the only way by which such a right can adequately be secured. At least an equal argument can be made for the "right" to food, clothing, shelter, warmth, access to the due process of law, and other basic essentials of civilized life, but it is remarkable that only with health and her handmaiden medicine is the right of access and possession equated with a particular socio-political approach. On a basis of daily needs much more of a case can be made for the provision of food by such means, hunger arising more predictably than sickness, but we have yet to hear a proposal for "the right to food" being supplied by such means. The implication is that the right to health is different in some way from these other rights, either in kind or in degree, as a more convenient place to begin, politically. If the former assumption is true, it deserves explanation; if the latter, the implications raised are very far-reaching in terms of the organization of our society.

It is a small insult to the intelligence of his readers that Dr. Macleod emotionalizes this point with word pictures of preventable dying in mothers and avoidable crippling in children. Most of us know, and regret, these unfortunates, as we do the neglected aged, the ill-treated children, the deprived minorities, the wreckage of road casualties and drug addiction, and the other unfortunates whom our much vaunted civilization fails to protect or succour. But the reasoned consideration of health needs and the best means and order of fulfilling them is not served by such an approach, nor by the implication that all charity and kindliness are the prerogatives of those with particular political beliefs.

It is therefore necessary to examine how the "right to health" may be defined, and having been defined, how it may best be supplied. In Dr. Macleod's thesis there is but one answer to the second part of the question, the first having been largely left in abeyance; health needs can be adequately supplied only through a universal, compulsory, government-controlled plan. The advantages which it is believed will accrue from this include the central and overall assessment of health needs, and the supply, organization and distribution of services to meet them. Many of us have had experience of government planning, in the field of health and in other areas, and there is little evidence that because a thing is done by a monopolistic government agency it is done better, more speedily, more efficiently, more thoroughly and more humanely. Many believe that, governed by those Laws so admirably elucidated by Professor Parkinson, central government monopoly more usually makes for tardiness, bumbledom, inefficiency and inhumanity, and many doctors are now in Canada because personal experience has reinforced these beliefs to the point of emigration. It has also been the experience of those countries in which social security legislation has been far extended that the comprehensiveness of these schemes tends to reside more in the minds of their planners, and in administrative tidiness, than in the relief of human needs. Certainly they leave many lacunae which are difficult to fill, on the one hand because charity has redirected its attention from a field thought to be in other hands, and on the other because of the reluctance of the official mind to admit the possibility of gaps in The Plan.

In the organization of our society as it finds itself at present, one of the basic assumptions is that no one should be permitted by accident or misfortune to fall beneath a decent standard of life. We have carried this belief so far in the face of human cupidity that it is probable that many are in receipt of relief who could well fend for themselves. Most also believe that people should be encouraged to rise above a minimum standard by their own legitimate efforts; and that personal and family income is best disbursed on a basis of personal and family responsibility, because of infinitely varying individual needs and desires. Governments have made many incursions into the field of personal responsibility, and there are many opinions as to their several justification, and as to how far a possible gain in security outweighs a certain loss of freedom. To request or permit a government agency to take over a portion of one's personal life and responsibilities reflects a conviction of personal incompetence which is regrettable, and of the higher wisdom of central corporate agencies which is certainly not justifiable by experience.

There are many possible alternatives to central compulsory government-controlled health insurance, which are impossible to detail here. One is based on the premise that it is the duty of the citizen to be insured against certain eventualities, but that he is free to seek the most individually appropriate cover above a defined minimum. Such a premise is frequently and successfully applied to automobile insurance, but the analogy is inadequate in that operation of an auto-

mobile is a voluntary matter, and the onset of illness is usually not. There is in such a scheme, be it non-profit making, a legitimate place for government participation, to pay the premiums for those who cannot pay them themselves. There is also a place for government participation in control, which might take the form of representation on a board and in the public presentation and auditing of accounts. Obviously such a scheme would lack the superficial unity and tidiness of Dr. Macleod's proposed alternative. However, an appearance of inefficiency is one of the penalties of democracy, but it has the compensation that the performance of dictatorships and bureaucracies has frequently proved even more inefficient.

Another concept that recurs in Dr. Macleod's article is that the patient is rarely competent to assess his own health needs, or the best means of supplying them. This may well be true, but basically one's health is one's own, to govern as one pleases provided others are not offended or endangered; and we have yet to see "the right to health" transmitted into "the duty to be healthy". Having listed many of the ways in which he feels this lack of judgment is manifest he says, "Everyone of these features adds unnecessarily to the cost of those essential services." The implication is not clearly stated, but one infers that health needs are better assessed by someone other than the patient, or, I suspect, other than his doctor. Here again it seems that Dr. Macleod hears the siren song of the rational organization of services by a central agency. That where such services have been established, better and more comprehensive health care is enjoyed, is at least open to doubt. No one can tell what would have emerged in the absence of the central agency, but experience with the British National Health Service, which could not build a single new general hospital in the first ten years of its operation; and present experience in Saskatchewan, with an arbitrary limit on hospital expenditure, and lack of geriatric and mental hospital accommodation-these do not unequivocally support the belief in the superior wisdom of a central monopoly. Wherever the so-called comprehensive health plans have been introduced, and freedom of action for the patient remained, there has become evident a demand for facilities not supplied by The Plan. Human beings are incorrigibly individualistic, and unwilling to believe that someone else always knows what is best for them, though they can be seduced into this belief for long periods by suitable combinations of threats and promises.

Other fundamental considerations must be faced when, and preferably before, health is organized nationally and compulsorily. As Dr. Macleod states, "What proportion of our gross national product should be devoted to health needs depends on our scale of values. Political judgment will have to settle the competition between measures which promote the welfare of the population, our commitments internationally and frills." One must add that political judgment must also necessarily decide what is which. In other words, health will be competing with railways, roads, defence, housing, and all other government activities for money, and the individual will largely have abrogated his decision as to what his health needs are to the mature (and untrained) wisdom of his political representatives. There are many politicians I should like to treat, but very few I should like to be treated by.

The implications for the doctor in any such scheme have been vehemently discussed, but little understood. Setting aside the wrangles on matters of service and payment, which appear to be inseparable from any such organization, there is the fundamental and triangular relationship between the doctor, his employer and his patient. If a doctor enters such a universal, compulsory, government-controlled scheme, he has deprived himself at one stroke of all negotiating power with his employer unless backed by strike or resignation. He cannot seek employment outside the Scheme, because it is a monopoly; and if medicine is permitted to exist outside the Service, it will be severely limited by the understandable reluctance of most patients to pay a second time for that for which they have already been charged. In the Scheme, he is morally compelled to continue to treat his patients if they need him, whatever his personal dissatisfactions, and what government will negotiate other than tardily and in poor faith, if they know that, whatever the prevarications, essential services will be maintained? The whole history of the British National Health Service in its relationship with its professional employees can be read as an exercise in the application of these and other principles of negotiation-notably also "divide and rule".

There is also the difference in attitudes between the doctor and politician, superbly expressed recently by a member of the latter group.\(^1\) "The politician practices the subordination of individual judgment; the doctor \(.\) glories in it." Again, "The doctor takes his decisions as an individual on his own single and ultimately unsharable responsibility. The politician is in the opposite case. \(.\) He cannot, so to speak, prescribe medicine for a patient unless \(.\) the Party agrees, nor can he institute a course of treatment unless the majority votes for it." Is it really possible for one group to practise medicine as we know it while under the control of the other? Is it not inevitable that treatment is going "to be postponed until the majority votes for it"?

The continuity of medicine depends on its continuing to attract the best young men and women. But to invite any young man to enter medicine now is to ask him to commit himself and his family to a future of which little can be discerned, and that little, depressing; to sell him a bill of goods with no promise as to how, if, or when he shall be paid. It seems germane that those concerned with medical education should try to discover what are the factors in medicine which have attracted, and keep, its present practitioners. Having done this, they should enquire as to what are the factors failing to attract students of requisite calibre and sufficient numbers to the medical schools today. It is at least possible that there may be some connection. Medicine has, for better or worse, come into the purview of the politicians, and when or if it will emerge from their consideration we do not know. If medicine must be considered politically, it is better that this should be done by establishing needs, and the means of filling them, rather than leaping on a band-waggon designed for vote-catching and tastefully emblazoned "The Right to Health". Health may be too serious a matter to be left to the doctors; it is also too vital to be played with by the politicians.

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Saskatoon, Sask.

#### REFERENCE

## MEDICAL NEWS IN BRIEF

# ACUTE RENAL INSUFFICIENCY AFTER INGESTION OF A GALLBLADDER DYE

Renal complications occurring after the ingestion of cholecystographic media are a great rarity. To date only two such cases have been reported and these were with iopanoic acid (Telepaque). Blythe and Woods in the New England Journal of Medicine (264: 1045, 1961) report the first case in which acute renal insufficiency occurred after the ingestion of a new gallbladder dye, bunamiodyl (Orabilex). Although obviously extremely rare, the possibility that acute renal insufficiency can complicate cholecystography should be kept in mind. Patients subjected to the test should be observed for 48 hours at least. There is no definite evidence that patients with chronic renal disease are more susceptible to this complication, but it seems reasonable to administer double doses of cholecystographic media with extreme caution.

### NEURO-ALLERGIC COMPLICATION AFTER IMMUNIZATION AGAINST POLIOMYELITIS

Side effects caused by immunization against poliomyelitis are extremely rare. According to Falk and Hinrichs (*Wien. klin. Wchnschr.*, 73: 277, 1961), the following case is the first serious complication of this nature observed in Austria.

About three weeks after the second dose of poliomyelitis vaccine (Salk) a 3-year-old healthy girl developed soreness in her legs, a low-grade fever and fatigue. Increasing severity of her symptoms led to hospitalization. On admission the child was unable to sit or stand. The positive findings included generalized hyperesthesia, nuchal rigidity, weak patellar reflexes and marked reduction of muscle strength, so that she was unable to hold a spoon. The cerebrospinal fluid contained 100 mg. % of protein but no cells. While virus studies, bacterial cultures and antibody tests were under way, she was treated symptomatically, but her symptoms were progressive. Tendon reflexes became unobtainable, and the muscle weakness increased, further involving the extremities in a symmetrical fashion. Even though some of the patient's symptoms were suggestive of poliomyelitis, the diagnosis of a Guillain-Barré syndrome was made on the basis of the elevated protein level in the cerebrospinal fluid without a corresponding increase in cells.

Treatment with prednisolone (1.5 mg. per kg. of body weight daily) led to gradual improvement until the steroid was discontinued because of an intercurrent infection. Within 24 hours exacerbation of the symptoms occurred; resumption of medication was followed by prompt improvement. Her further course was uneventful; the patient's muscle strength returned slowly, and she was discharged asymptomatic after seven weeks.

The disease was considered a neuro-allergic condition caused by poliomyelitis vaccine. Similar cases have been reported in other countries. It is surprising that allergic reactions are not observed more often after immunization against poliomyelitis, for the vaccine con-

tains small amounts of penicillin, dihydrostreptomycin, proteins from monkey kidneys and preservatives such as merthiolate. The proteins especially are apt to stimulate the formation of antibodies.

The question has been raised whether it is possible to avoid these dangerous reactions. It appears to be of little help to exclude from immunization children with known allergic manifestations, as the majority of those who developed severe reactions had no previous history of allergy. The authors suggest that thorough observation for any transient allergic manifestations after the first dose of vaccine may help to reduce further the occurrence of serious neuro-allergic complications.

### WISSLER-FANCONI SYNDROME

Since his first description in 1943 of the clinical entity which he called "subsepsis allergica", H. Wissler has been able to observe personally 18 more cases; and 39 cases in all have appeared in the European literature. In the English-speaking countries, especially in the United States, this syndrome is not admitted as a distinct disease but is included in acute rheumatic fever because two of its main features, polyarthritis and erythema marginatum, are part of the cardinal criteria of Jones.

Two cases are described by Ferrier and Mégevand (Schweiz. med. Wchnschr., 91: 581, 1961), one of a 17-year-old male whose disease appeared to have started when he was 10 and was characterized by recurrent bouts of arthralgia without considerable swelling of the involved joints, with fever and with a skin erruption, sometimes of urticaria type, sometimes circinate, and always of short duration. Leukocytosis with neutrophilia was frequent, and steroids as well as salicylates acted relatively well on the acute phases of the disease, while penicillin prophylaxis had no preventive action. The second case was that of a 3-year-old girl who at the age of 23 months began having fever and rubeola-like eruption and recurring bouts of fever and eruption every few weeks. The condition failed to respond to administration of penicillin or wide-spectrum antibiotics. Laboratory findings were completely noncontributory, including an antistreptolysin titre determination and complement fixation tests. Relatively small doses of aspirin reduced temperature, improved the skin rash and slowed the very accelerated sedimentation rate. At no time during the nine weeks in hospital was there any obvious swelling of joints. Her heart did not show evidence of involvement at any time, and six months later the child was apparently

Discussing these and similar cases, the authors draw attention to similar episodes occurring shortly after injections of vaccines and in connection with the first exposure to tuberculosis. In one case a positive test to cold hemagglutinins was obtained.

Although the features of this condition are characteristic and entitle it to be isolated from the more typical cases of rheumatic fever, it is doubtful whether the name "subsepsis allergica" is accurate or useful.

(Continued on advertising page 18)

## ASSOCIATION NOTES

- I. SOME CHARACTERISTICS OF THE MEDICAL PROFESSION OF CANADA
- II. COMMENTS OF THE MEDICAL PROFESSION ON THE TERMS OF REFERENCE OF THE ROYAL COMMISSION ON HEALTH SERVICES

Preliminary submissions to the Royal Commission on Health Services by The Canadian Medical Association, C.M.A. House, 150 St. George St., Toronto 5, and L'Association des Médecins de Langue Française du Canada, 326 est, Boulevard Saint-Joseph, Montreal 14, September 27, 1961.

Presented by: Dr. G. W. Halpenny, President, The Canadian Medical Association, 1414 Drummond Street, Montreal 25. Dr. T. J. Quintin, Chairman of the General Council, The Canadian Medical Association, 422 London Street, Sherbrooke, P.Q. Dr. Jacques Léger, representing l'Association des Médecins de Langue Française du Canada, 3766 Queen Mary Road, Montreal. Dr. G. E. Wodehouse, Honorary Treasurer, The Canadian Medical Association, and Chairman, Executive Sub-Committee on Health Services, 284 St. Clair Avenue West, Toronto 7. Dr. J. A. McMillan, Member, Executive Sub-Committee on Health Services, Charlottetown Clinic, 1 Rockford Street, Charlottetown. Dr. L. R. Rabson, Member, Executive Sub-Committee on Health Services, Mall Medical Group, 280 Memorial Blvd., Winnipeg 1. Dr. A. D. Kelly, General Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5.

# I. SOME CHARACTERISTICS OF THE MEDICAL PROFESSION OF CANADA

Mr. Chairman and Members of the Royal Commission on Health Services:

- 1. This is a preliminary submission of the doctors of Canada and it is presented jointly by The Canadian Medical Association (15,131 members) and l'Association des Médecins de Langue Française du Canada (5300 members), for the purpose of acquainting the Royal Commission on Health Services with certain characteristics of the medical profession.
- 2. Since our request to the Prime Minister appears to have been instrumental in the decision to undertake this study of Canada's health services, we are gratified that your terms of reference permit the utmost latitude in your investigations. The very amplitude of your instructions conveys the impression of an awareness that no single element of health services can be considered in isolation but that each of the areas affects all others. It is further noteworthy that the concept of quality runs like a thread throughout your terms of reference. This is in accord with the basic belief of the medical profession and it will govern our subsequent submissions. It is hoped that time will be permitted for a truly comprehensive study.
- 3. In conformity with the constitutional and traditional responsibilities of the provinces in matters of

health, the basic organization of the medical profession is provincial. The Canadian Medical Association is a federation of ten provincial Divisions while the peripheral organization of l'Association des Médecins de Langue Française du Canada is based on five regional components. In the studies of this Royal Commission this will prove to be of more than theoretical interest since regional considerations are of prime importance.

- 4. We subscribe to the definition of health as stated in the preamble to the Charter of the World Health Organization, "Health is a state of physical, mental and social well-being and not merely the absence of disease and infirmity."
- 5. The promotion of health is the primary object and the daily duty of members of the medical profession. It would, however, be a mistake to assume that doctors and doctoring are themselves capable of satisfying the requirements for optimum health. The following paragraph from a 1949 Statement of Policy of The Canadian Medical Association is pertinent:
  - "Among the factors essential to the people's health are adequate nutrition, good housing and environmental conditions generally, facilities for education, exercise and leisure; and not least, wise and sensible conduct of the individual and his acceptance of personal responsibility."
- 6. Medicine is an ancient art and a science which is constantly adding to its body of knowledge. The profession is governed by a Code of Ethics and by law. In Canada such law is provincial legislation, established in the public interest to ensure that only qualified physicians, educated to a high standard, are admitted to the registers as medical practitioners.
- 7. Degrees in medicine are conferred by the Faculties of Medicine of twelve Canadian universities and the output of these schools (approximately 850 per year) is the principal source of additions to the ranks of physicians of all types. In preparation for a career in medicine, aspirants must meet high standards of preliminary education, take two to four years of university training in a pre-medical course and successfully complete four years of the medical course prior to the award of a degree. Before the granting of a licence to practise, the candidate must complete a satisfactory year of internship in an approved hospital and, in most provinces, must pass the examinations of the Medical Council of Canada.
- 8. From this point on, a great variety of careers are available to medically qualified persons. General or specialty practice, research, public health, occupational medicine, military medicine or medical administration attract those who develop special interests. In practically all instances, further postgraduate training is essential, and as an example of its extent, it is only necessary to mention that candidates for the Fellowship of the Royal College of Physicians and Surgeons of Canada in any one of 22 currently recognized specialties must have completed five years of approved training following graduation and then submit themselves to a final searching examination. A serious social consequence of this lengthy period of postgraduate training

is that the age of 30-32 has been attained before a specialist's productive work is commenced and before

he begins to become self-supporting.

9. Other authorities, including the Association of Canadian Medical Colleges, will present in greater detail the problem facing medical education in this country. We would remark, however, that the whole profession is aware of the fundamental importance of maintaining, expanding and constantly improving the basic training of the doctor. We are justifiably proud of the high standards of Canadian medical schools and we recognize that the future health of this country is in no small degree dependent on the contribution which they will make. It is our hope that this Royal Commission in all its deliberations and recommendations will keep in mind that nothing should be permitted to impede the task of medical education, medical recruitment and the attraction of a high quality of students to a career in medicine. Any new proposals should be designed to aid and foster the training and research which are so essential to continued progress.

10. A rough measure of adequacy of medical services is the physician-population ratio. During the period 1900-1950, the national ratio in Canada has been, with remarkable constancy, of the order of 1:980. We estimate that the current ratio is 1:888, a more favourable figure than we have ever enjoyed, and one which compares favourably with that of the more advanced countries of the Western world. It will be appreciated that ratios of the type mentioned here represent gross figures of medically qualified persons and that not all of the doctors are engaged in the care of patients. We are conscious, moreover, that medical immigration during the past ten years has contributed materially to Canada's medical manpower and that without this advantage, which may be temporary, the physician-population ratio would have deteriorated. In other words, we are not producing enough doctors in Canada to keep pace with our rapidly expanding population. The supply is just adequate under current conditions of practice and almost certainly would be inadequate to staff new and demanding areas of health services. We are conscious that the attractions of other pursuits, less demanding in time, money and effort than a career in medicine, are appealing to the bright minds among the youth of this country, and that medicine must compete actively for recruits to the profession.

11. Although the current gross figures on medical manpower are favourable, the distribution among the provinces shows unevenness. The urbanization of the medical profession is as evident as it is in the population generally. The effect has been a shortage of doctors in the sparsely settled hinterland and in rural communities. This is to some degree offset by the greater productivity of the individual doctor, particularly if he has the facilities of a hospital, and by increased mobility of patients due to improved transportation.

12. The physician's relationship to health services may be broadly divided into two main categories; firstly, services rendered to patients individually and directly under conditions of private practice as we know it, and secondly, services rendered indirectly or collectively. These two types of service are complementary and are essential to a well-balanced program.

13. The majority of Canadian doctors conduct private practice as individuals or as members of groups for the rendering of personal health services to patients who seek their aid. Implicit in the concept of private prac-

tice is the freedom of the doctor to decide where and in what field of medicine he chooses to establish himself and, equally, the freedom of the patient to choose his medical attendant. It is our view that under these conditions, medical services of the highest quality pertain and that the factors which operate to achieve the distribution of physicians with appropriate qualifications have been generally in the public interest. Methods of financing personal health services should not be permitted to affect the quality of private practice adversely and it is our experience that they need not do so. Fees for professional services rendered constitute for patients and doctors alike the most widely accepted method of remunerating physicians in this category.

14. The rendering of health services indirectly or collectively constitutes the other broad area of health services and many Canadian doctors are so engaged. In this category we place many of the physicians engaged in public health and preventive medicine at all levels of government services, the industrial physicians, the insurance medical officers, the pathologists, the bacteriologists, the biochemists, the radiologists under certain conditions, the physiatrists, the research workers, the teachers of medicine, particularly in the pre-clinical subjects, the doctors providing services in mental hospitals, sanatoria, rehabilitation centres, the hospital and institutional medical administrators and others who are difficult to classify. Although some of these physicians are directly involved in the clinical management of individual patients, they are distinguished from private practitioners by the fact that free choice of doctor and patient does not apply to their work to the same degree. Many of the medical workers in this category appear to be best remunerated by salary, although to others fees for services rendered may represent the method of choice. In some instances a combination of these methods provides a satisfactory solution.

15. The mutual confidence of doctor and patient is an important element in successful therapy and in the quality of medical care rendered. The term doctorpatient relationship is used to describe a complex of interacting forces which include elements of choice, trust, interest, responsibility, sympathy and rapport. Where a good doctor-patient relationship exists the patient is likely to obtain the optimum benefit from his physician's services. In its absence, the art of medicine is difficult to apply and the technical and mechanical aspects of therapy are no substitutes. Regardless of the methods of providing for the rendering of clinical services, the reality and the value of good doctor-patient relationships should be recognized.

16. The work of doctors in the modern approach to health services is supplemented and amplified by a host of paramedical workers. It is a cliché to assert that modern medicine demands a "team approach", but it carries some validity when one considers the skills represented in the following list of occupations closely related to medicine: dentists, veterinarians, nurses, sanitary engineers, hospital administrators, pharmacists, laboratory technologists, radiological technicians, nurses' aides, dietitians, sanitary inspectors, medical social workers, medical record librarians, health educators, psychologists, physiotherapists, occupational therapists, speech therapists, optometrists, chiropodists and inhalation therapists.

17. In the public interest the medical profession is governed in a legal sense by provincial statutory bodies, usually called Colleges of Physicians and Surgeons of

the province concerned. The Medical Acts or the Medical Profession Acts of the Canadian provinces establish Councils which prescribe the qualifications required for admission to the Register, which is a list of registered medical practitioners, promulgated basically to permit the public to distinguish qualified doctors of medicine from others. The process of registration is unofficially referred to as medical licensure, and graduates of Canadian medical schools are required by most provinces to pass the examinations of the Medical Council of Canada in addition to their university examinations and to serve a year's internship before being eligible for registration. Graduates of non-Canadian schools are required also to pass the examinations of the Medical Council of Canada and to fulfil other provincial requirements. A major exception is that practi-tioners registered on the "home list" of the General Medical Council of Great Britain may register by a reciprocal arrangement without further examination in Alberta, Saskatchewan, Manitoba, Nova Scotia, Prince Edward Island and Newfoundland. Reference has previously been made to the effect of immigration on Canada's current medical manpower. A major proportion of the immigrant registrants have been from the United Kindom. The remainder of these admissions to our medical registers come from many different countries. Our preliminary appraisal of Canada's need for doctors will shortly be filed and we have gladly accepted the recent invitation of the Royal Commission to conduct a detailed study of medical manpower in all its aspects.

18. Again in the public interest, the provincial medical licensing authorities have considerable disciplinary powers over registered medical practitioners, extending to the ultimate penalty of erasure from the register for serious professional misconduct.

19. The profession exercises a considerable degree of self-discipline in many other directions. The Canadian Medical Association promulgates a Code of Ethics which is a guide to the medical profession on behaviour and etiquette based on the age-old traditions of medicine brought up to date and constantly reviewed and interpreted.

20. Since an important part of the doctor's work is carried out in hospitals, the highest standards of patient care are promoted by self-imposed rules elaborated by the medical staffs of these institutions. These include the voluntary services of doctors on Credential Committees which scrutinize the training and experience of applicants for hospital staff privileges and assign or restrict such privileges on the basis of their assessments. Having received certain privileges, the performance of a medical staff member is subject to continuing scrutiny. Tissue Committees review the pathological reports of tissues taken at operation to check the indications for surgery. Admission and Discharge Committees ensure the efficient use of hospital beds, and Record Committees see to it that essential data of the patients' experience are promptly recorded. Medical Audits and Professional Activity Studies are modern devices used to assess the quality of medical services in hospitals.

21. The Canadian Council on Hospital Accreditation is a national organization devoted to maintaining and promoting the highest standards of patient care. Membership is representative of the Canadian Hospital Association, the Royal College of Physicians and Surgeons of Canada, l'Association des Médecins de Langue Française du Canada and The Canadian Medical Association. The work of the Council is financed by contributions from these bodies and recently by contributions

from nine provincial governments.

22. The voluntary bodies of organized medicine are represented nationally by two basic organizations, The Canadian Medical Association and l'Association des Médecins de Langue Française du Canada. Membership in these Associations is not a requirement for practice, and their strength and usefulness are derived from the interest of individual doctors who support their activities. Many Canadian doctors are members of both of these national organizations.

23. L'Association des Médecins de Langue Française du Canada is national in scope, comprising five divisions or "Filiales": Western Provinces, Ontario, Quebec, New

Brunswick and Nova Scotia.

24. The Charter states its purpose as follows:

"Elle a été formée dans les buts suivants: Rallier sur un terrain commun, culturel et professionnel, les médecins de langue française du Canada, organiser des congrès scientifiques; publier des revues et périodiques médicaux et scientifiques; sauvegarder les interêts professionnels de ses membres; encourager ou établir d'autres œuvres analogues."

25. The Canadian Medical Association is a federation of ten provincial Divisions, each autonomous in its own sphere but combining to form the largest medical organization in this country. The Royal Commission will receive briefs and submissions from the provincial Divisions of the C.M.A. and doubtless from other provincial medical organizations. It is unnecessary to elaborate that these provincial submissions will be of fundamental importance to the studies of the Commission because health in the Canadian context is primarily of provincial concern and because the health problems peculiar to our geographic regions will be

26. The functions of the C.M.A. are broadly covered by the following extract from the Act of Incorporation as amended in 1959:

"The objects of The Association shall be:

(a) to promote the medical and related arts and sciences and to maintain the honour and the interests of the medical profession;

(b) to aid in the furtherance of measures designed to improve the public health and to prevent disease

and disability;

(c) to promote the improvement of medical services however rendered;

(d) to publish the Canadian Medical Association Journal and such other periodic journals as may be authorized, together with such transactions, reports, books, brochures or other papers as may promote the objects of The Association;

e) to assist in the promotion of measures designed to improve standards of hospital and medical services;

- (f) to promote the interests of the members of The Association and to act on their behalf in the promotion
- (g) to grant sums of money out of the funds of The Association for the furtherance of these objects; and
- (h) to do such other lawful things as are incidental or conducive to the attainment of the above objects.
- 27. As in most voluntary Associations, the work in the C.M.A. is carried out by committees which are as representative as possible of the regions of the country

and of the gradations of professional opinion. To indicate the range of our interests, the following partial list of committees is recorded:

Advisory Committee to the Federal Government; Committee on Approval of Hospitals for the Training of Junior Interns; Committee on Approval of Schools for Laboratory Technologists; Committee on Approval of Schools for Radiological Technicians; Committee on Awards, Scholarships and Lectures; Committee on Cancer; Committee on Child Health; Committee on Economics; Committee on Ethics; Committee on Hospital Service and Accreditation; Committee on Occupational Medicine; Committee on Maternal Welfare; Committee on Medical Education; Committee on the Medical Aspects of Traffic Accidents; Committee on Nutrition; Committee on Pharmacy; Committee on Prepaid Medical Care; Committee on Public Health; Committee on Public Relations; Committee on Rehabilitation.

28. In addition to the large general medical Associations, the special and sectional interests of the medical profession are represented by the following national medical societies all of which are affiliated with The Canadian Medical Association: Canadian Academy of Allergy, Canadian Anaesthetists' Society, Canadian Association of Pathologists, Canadian Association of Physical Medicine and Rehabilitation, Canadian Dermatological Association, Canadian Heart Association, Canadian Medical Protective Association, Canadian Neurological Society, Canadian Ophthalmological Society, Canadian Orthopaedic Association, Canadian Otolaryngological Society, Canadian Paediatric Society, Medical Section of the Canadian Pharmaceutical Manufacturers' Association, Canadian Psychiatric Association, Canadian Rheumatism Association, Canadian Thoracic Society, Canadian Urological Association, College of General Practice of Canada, The Royal College of Physicians and Surgeons of Canada, Society of Obstetricians and Gynaecologists of Canada, The Canadian Association of Radiologists, and The Canadian Life Insurance Medical Officers Association.

29. It is our hope and expectation that many of them will elaborate for the Royal Commission on Health Services important matters in their fields of interest which may be mentioned only briefly in our submissions.

30. In addition to the national medical societies affiliated with the C.M.A. there are certain organizations of mixed lay and medical membership devoted to the promotion of health in the special fields of their interest. The following is a list of such Canadian organizations which are affiliated with the C.M.A.: Canadian Arthritis and Rheumatism Society, Canadian Association of Medical Record Librarians, Canadian Cancer Society, Canadian Council for Crippled Children and Adults, Canadian Mental Health Association, Canadian Nurses' Association, Canadian Tuberculosis Association, Health League of Canada, National Heart Foundation, Priory in Canada of the Grand Priory in the British Realm of the Venerable Order of the Hospital of St. John of Jerusalem, The Canadian Diabetic Association, The Canadian Hearing Society, The Canadian Society of Laboratory Technologists, Victorian Order of Nurses for Canada.

31. The relationship of the medical profession to many other health agencies is intimate and co-operative, and an interchange of representatives is carried out with the Association of Canadian Medical Colleges, the Canadian Hospital Association, the Canadian Red Cross Society and the National Cancer Institute of Canada. In the international sphere the C.M.A. is a member organization of the World Medical Association.

32. It may be inferred that the organization of the medical profession and the scientific developments of the last fifty years have enhanced the ability of doctors to provide more and better health services. The results are attested by the reduction in mortality and morbidity from a wide variety of diseases and in the steadily increasing span of life. Paradoxically, this has not resulted in a decrease but in a substantial increase in the demand for medical services. The care of a steadily increasing number of persons who are afflicted with chronic illnesses and with the physical and mental consequences of growing old presents a major problem. The provision of facilities and personnel to provide convalescent care and medical rehabilitation will assume greater importance than has been apparent in the past.

33. The increase in scientific knowledge has affected the whole structure of medical education and has accelerated the process of specialization. In a profession which demands a high standard of competence from its members, medicine has truly become a lifelong study so that the efforts of most of the organizations of doctors are directed towards educational activities to enable their members to learn and to apply the new knowledge which is constantly becoming available.

edge which is constantly becoming available.

34. Postgraduate education for purposes of licensure or approved specialist certification is provided in a carefully selected group of hospitals and medical centres. Continuing postgraduate education is available in the form of refresher courses, and at scientific sessions organized in conjunction with meetings of hospital staffs and of medical societies and associations varying from local to national in their scope. In addition, aids to education such as television, motion pictures, taped teaching material and scientific exhibits, are all used to refresh and improve the doctor's knowledge for the ultimate benefit of his patients.

35. Medical journals also play a very important part in the dissemination of scientific knowledge. The world's medical literature in the form of periodic publications has attained a volume and a quality which is astonishing. In Canada, the Canadian Medical Association Journal and l'Union Médicale du Canada are representative of the general medical journals publishing original work of Canadian authors. There are at least eight Canadian journals devoted to material in special fields of medicine and a host of reviews, bulletins, abstract journals and other publications all of which contribute substantially to the doctor's continuing education.

36. Good medical care is that ordinarily provided by the well-trained and conscientious physician. It is limited to the practice of rational medicine based on the medical sciences and the age-old arts of the profession. There is no place in good medical care for the quack, the cultist or the magician. In pursuit of its objective of "recommending methods of ensuring the best possible health care" the Royal Commission should not be diverted by the claims of the pseudo-scientific cults whose systems and theories are not represented in the curricula of any university or institution of higher learning.

37. The scope of publicly financed health services in Canada will doubtless impress the Royal Commission as its studies progress. Suffice it to say that we in

Canada have accepted a large element of government participation in the provision of health services. In many instances these services were established at the instigation and urging of the medical profession and in all instances they are staffed by colleagues whom we undertake to represent. In the relatively restricted field of the Federal authority it is worthy of mention that medical services are provided under the Department of Veterans' Affairs, the Department of National Defence and through the Department of National Health and Welfare. Divisions of the latter administer the Immigration and Sick Mariners' Medical Service and the Indian and Northern Health Services. The system of National Health Grants, the very large contribution to hospital insurance and the recent substantial support given to medical research through the Medical Research Council are examples of the application of tax dollars to our field of interest.

38. It is, however, in the realm of the provinces that the public financing of collective health services is seen in its fullest development. The whole field of public health, the mental health services, the control of tuberculosis and in some provinces the diagnosis and treatment of cancer, have been assumed. While the Federal Government makes very substantial monetary and other contributions to hospitalization insurance, the administration and a large portion of the cost have become provincial responsibilities. Measures to promote the rehabilitation of the sick and injured have been sponsored and supported. Further examples of the institutional care of whole segments of the population will be seen in certain provinces.

39. Doctors have long recognized that patients should be able to budget for their expenditures on medical services in the same way as they budget for other essential needs. As a result, the medical profession of Canada has organized agencies for the application of insurance procedures to the distribution of medical services. As early as 1937 the first non-profit plans of prepaid medical care were established by the provincial Divisions of the C.M.A. and today eleven such plans, organized, sponsored and fostered by the profession, provide medical services insurance to over four million Canadians. In the immediate post-war period it was apparent that these plans of voluntary health insurance established under our auspices required to be organized nationally. A series of conferences called by The Canadian Medical Association resulted, in 1951, in the formation of Trans-Canada Medical Plans. The governing body of T.C.M.P. is representative of The Canadian Medical Association and the following member plans, which are sponsored by the profession, and provide medical services insurance primarily in the provinces indicated:

Maritime Medical Care Incorporated (Nova Scotia); Maritime Hospital Service Association (New Brunswick, Prince Edward Island, Newfoundland); Quebec Hospital Service Association (Quebec); Physicians' Services Incorporated (Ontario); Windsor Medical Services, Incorporated (Ontario); Manitoba Medical Service (Manitoba); Medical Services Incorporated (Saskatchewan); Group Medical Services (Saskatchewan); Medical Services (Alberta) Incorporated (Alberta); Medical Services Association (British Columbia); and B.C. Medical Services Incorporated (British Columbia).

40. In addition to the plans of prepaid medical care established under our own auspices, a variety of organizations, chiefly the licensed insurance companies of Canada, provide insurance coverage to a further four million Canadians. We have worked closely with these agencies and in the process have gained a knowledge of the merits of their approach to a common problem.

41. Similarly, the profession has since 1935 cooperated with provincial governments in the provision of medical care to the recipients of public assistance. Such plans, basically financed with public funds but heavily subsidized by the profession, now operate in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario and Nova Scotia.

42. The experience of the doctors of Canada in cooperating with governments in the provision of health services and their participation in medical insurance plans of all types has led to certain conclusions which were expressed in June 1960 in the following C.M.A. Statement on Medical Services Insurance which has subsequently been endorsed by l'A.M.L.F.C. and thus represents the collective viewpoint of the medical profession of Canada:

"The Canadian Medical Association believes that: The highest standard of medical services should be available to every resident of Canada.

Insurance to prepay the costs of medical services should be available to all regardless of age, state of health or financial status.

Certain individuals require assistance to pay medical services insurance costs.

The efforts of organized medicine, governments and all other interested bodies should be coordinated towards these ends.

While there are certain aspects of medical services in which tax-supported programs are necessary, a tax-supported comprehensive program, compulsory for all, is neither necessary nor desirable.

43. "The Canadian Medical Association will support any program of medical services insurance which adheres to the following principles:

1. That all persons rendering services are legally qualified physicians and surgeons.

2. That every resident of Canada is free to select his doctor and that each doctor is free to choose his patients.

3. That the competence and ability of any doctor is determined only by professional self-government.

- 4. That within his competence, each physician has the privilege to treat his patients in and out of hospital.
- 5. That each individual physician is free to select the type and location of his practice.
- 6. That each patient has the right to have all information pertaining to his medical condition kept confidential except where the public interest is
- 7. That the duty of the physician to his individual patient takes precedence over his obligations to any medical services insurance programs.
- 8. That every resident of Canada, whether a recipient or provider of services, has the right of recourse to the courts in all disputes.
- 9. That medical services insurance programs do not in any way preclude the private practice of medicine.

- That medical research and undergraduate and postgraduate teaching are not inhibited by any medical services insurance program.
- 11. That the administration and finances of medical services insurance programs are completely separate from other programs, and that any board, commission or agency set up to administer any medical services insurance program has fiscal authority and autonomy.\*
- 12. That the composite opinion of the appropriate body of the medical profession is considered and the medical profession adequately represented on any board, commission or agency set up to plan, to establish policy or to direct administration for any medical services insurance program.
- 13. That members of the medical profession, as the providers of medical services, have the right to determine the method of their remuneration.
- 14. That the amount of remuneration is a matter for negotiation between the physician and his patient, or those acting on their behalf; and that all medical services programs make provisions for periodic or automatic changes in remuneration to reflect changes in economic conditions."
- 44. The foregoing description of the medical profession of Canada in general terms is designed to acquaint the Royal Commission on Health Services with certain characteristics of the doctors' part in health services and to establish our right to speak for the profession.
- 45. It should be apparent that the physician performs a function which is socially useful and which has as its central motive his obligation to promote the welfare of the patient. Doctors as individuals and as citizens have certain rights which should be recognized and preserved. These include the right to organize for his own protection and for the promotion of his interests; the right to exercise freedom of choice with respect to the type of work which he undertakes and the location in which he performs it; the right to accept or reject individual patients subject only to emergent and humanitarian considerations; the right to participate in or abstain from any plan of medical services insurance; the right to determine the method of his remuneration and, subject to the controls imposed by law and by his colleagues, to manage all aspects of his patients' disabilities within his competence.
- 46. The medical profession is aware that in addition to the rights here mentioned the doctor has an obligation to keep his knowledge in good repair, to bring to the service of his patient his undivided attention and his best efforts, to seek the aid of colleagues when the patient's condition demands skills beyond his capacity and experience and, in general, strive to apply with kindness and humanity all the resources of his profession for the well-being of his patient.
- 47. As stated at the outset, this is a preliminary general submission of the medical profession. We will file further specific data and recommendations as the studies of the Royal Commission on Health Services proceed.

### II. COMMENTS OF THE MEDICAL PROFESSION ON THE TERMS OF REFERENCE OF THE ROYAL COMMISSION ON HEALTH SERVICES

The medical profession is glad to take advantage of the invitation conveyed in the notice of this preliminary hearing to the effect that "this Commission welcomes from the start suggestions from the public relating to the scope of its enquiry."

In this analysis of your Terms of Reference we undertake to call to your attention those factors which seem to us appropriate in the comprehensive study of present and future health services in Canada which you will undertake. Your remit portrays your task in broad terms in the first paragraph of the Order-in-Council which establishes this Commission, where it is stated "it is considered to be in the public interest to have a comprehensive and independent study made of the needs of the Canadian people for health services and the resources available to meet such needs with a view to recommending methods of ensuring that the best possible health care is available to all Canadians."

The medical profession would endorse this objective and would offer its aid in assisting you in any studies which you will undertake.

We note with approval that the concept of quality is evident in the language of your instructions; "improving", "best possible", "adequate", "a high rate of scientific development" are phrases which strike a responsive note with doctors and our contributions to your studies will be framed with this in mind.

In respect of the specific terms of reference we have undertaken to provide headings which indicate to us appropriate subjects for study by the Commission. The list is as exhaustive as possible but it will doubtless be amplified as your hearings proceed and as other interested parties provide you with their interpretation of the scope of your enquiry.

(a) "The Existing Facilities and Methods for Providing Personal Health Services Including Prevention, Diagnosis, Treatment and Rehabilitation"

(We distinguish between the use of the word "facilities" in term (a) and term (f). In the former instance we interpret the word to refer to means of facilitating health services and in the latter, to physical facilities).

- I. Private Medical Practice as a Facility and Method of Providing Personal Health Services
- 1. Private practice represents the major method by which personal health services are provided in Canada today. The evolution of private practice has proceeded far from the concept of the doctor whose resources were contained in his head and his little black bag. The effect of specialization, better diagnostic and therapeutic equipment, the employment of paramedical personnel, progress in hospital and other institutional developments and professional and public education have all enhanced the services which the private practitioner is able to furnish. Scientific advances, communications and transportation have all improved the quality and availability of private medical practice.

2. Patterns of Practice-

(a) Family physician or general practitioner

(b) Specialist: (1) distribution, (2) efficient use of special equipment, (3) consultations and referrals.

Both the family physician and the specialist may provide his services as an individual or as a member of a group.

3. Essentials of Private Practice-

 (a) Personal responsibility of physician to his patient.

(b) Freedom of patient to choose and change his medical attendant.

(c) Freedom of doctor to choose type and location of practice.

4. The evolution and growth of specialism.

5. The identification, training and utilization of paramedical personnel.

The function of the private practitioner in prevention, diagnosis, treatment and rehabilitation.

7. The role of the private practitioner and the philosophy of the medical profession in the development of voluntary insurance for medical services:

(a) Sponsorship by the profession.

(b) Role of prepaid medical care plans as insurance mechanisms.

(c) Support by the profession who exercise controls.

(d) The status of the subscriber remains as a private patient.

private patient.

(e) The voluntary coverage of persons by: (1) TCMP plans; (2) Commercial carriers; (3) Co-ops.; (4) Company or union-operated plans; (5) Municipal plans.

8. The role of the private practitioner in industrial health programs.

9. The relationship of private practice to health services and facilities provided by voluntary agencies in prevention, diagnosis, treatment, rehabilitation and research:

(a) The area of co-operation.

(b) The assistance provided by paramedical personnel.

(c) The flexibility of voluntary agencies.

(d) The role of the voluntary agencies in the training of specialists.

10. The operation of voluntary insurance in the provision of extended health benefits for paramedical services, disability insurance and out-of-work benefits.

### II. Governmental Agencies

Many services provided by governmental agencies were developed at the request of the medical profession to meet specific needs. In almost all areas private practitioners play a substantial part in the implementation of these programs, i.e. they are provided in part by full-time physicians and in equal or greater amount by physicians in private practice.

- 1. Health Services administered and financed by the Federal Government
- (a) Indian and Northern Health Services

(b) D.V.A.

(c) Immigration and Sick Mariners Service

(d) Armed Forces

(e) Other federal responsibilities-e.g. R.C.M.P.

(f) Consultant services

(g) Medical services in federal penitentiaries

(h) Other

2. Health Services financed but not administered by the Federal Government

(1) National Health Grants:

(a) The National Health Grants program amounts available and areas covered.

(b) Utilization by provinces.

(2) Medical Services Insurance:

 (a) Medical insurance coverage for employees of federal departments.

(b) Medical insurance coverage for dependants of Armed Services personnel, dependants of R.C.M.P., etc.

- 3. Health Services administered and financed by provincial and/or municipal Governments
  - (1) Public health services:

(a) Preventive medicine

(b) Environmental hygiene and sanitation

(c) Other.

- (2) Mental health services
- (3) Tuberculosis control

(4) Cancer programs

- (5) Alcohol and drug addiction
- (6) Provincial laboratories

(7) Provision of biologicals

(8) Venereal disease-treatment and control

(9) Other.

- 4. Health Services financed but not administered by Provincial Governments
  - (1) Social assistance medical services programs
  - (2) Medical services for chronically ill, including rehabilitation
  - (3) Blood transfusion services (C.R.C.)

(4) Other.

- 5. Health Services Programs administered by Provincial Boards but not financed by the Provinces
  - (1) Workmen's Compensation Board

(2) Other.

- 6. The Hospital as an element of modern Medical Care
  - (1) Active treatment hospitals

(2) Convalescent hospitals

(3) Chronic hospitals

(4) Diagnostic services

(5) Outpatient and emergency services

(6) Alternate care programs, e.g. home care programs and homes for the aged

(7) Special treatment facilities, e.g.:

- (a) Cardiovascular units
- (b) Therapeutic radiology

(c) Radio-isotopes

- (d) Rehabilitation
- (e) Artificial kidney or other special units

(f) Other.

- 7. The Hospital Insurance and Diagnostic Services Act
- (a) History and current operation

(b) Its effect on:

(Continued on page 810)



# LOMOTIL

(brand of diphenoxylate hydrochloride with atropine sulfate)



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Descriptive literature and directions for use available in 247 QUEEN ST., E., BRAMPTON, ONT. Physicians' Product Brochure No. 81.

Research in the Service of Medicine

(Continued from page 808)

- (1) Hospital costs
- (2) Availability of beds
- (3) Medical practice
- (4) Quality of medical care
- (5) Undergraduate and postgraduate medical education
- (6) Clinical research.

### III. Drugs and Appliances Provided by:

- Private purchase: (a) Doctor-prescribed; (b) Self-medication
- 2. Government-provided
- 3. Provided through voluntary organizations.

### IV. Preventive, Diagnostic, Therapeutic and Rehabilitative Services

Correlation of existing services under the facilities mentioned in this term of reference.

# (b) "METHODS OF IMPROVING SUCH HEALTH SERVICES"

Under this heading the Commission and interested organizations should analyze the adequacy of the services set out under the first term of reference, comment on any deficiencies noted and recommend actions which should be taken to correct these deficiencies, including the extension of medical services insurance to those not now insurable. Discussion of physical facilities should be deferred as it relates to term (f).

# (c) "THE CORRELATION OF ANY NEW OR IMPROVED PROGRAM WITH EXISTING SERVICES WITH A VIEW TO PROVIDING IMPROVED HEALTH SERVICES"

This term relates in part to the services and agencies mentioned in (a) and (b) insofar as they may require integration, correlation and the elimination of duplication.

However, it affords the opportunity to project possible developments of the future. Many of these may be dependent on new scientific discoveries and their application, and the trend is impossible to predict with accuracy. Health services now in the early stages of their development should be studied. Included in this category would be geriatric services, home nursing and homemaker programs, control of alcoholism, prevention and control of accidents and poisoning, the medical aspects of traffic accidents and programs to promote healthful recreation and physical fitness.

### (d) "The Present and Future Requirements of Personnel to Provide Health Services"

The C.M.A. will file a study of medical manpower projected to 1980. It portrays the need for a considerable amplification of the facilities of Canada's existing medical schools and for the establishment of new Faculties of Medicine.

An endeavour should and will be made to define the need of specialists by category and to portray the postgraduate educational facilities required to train them.

Similar studies on the paramedical personnel would be desirable.

# (e) "METHODS OF PROVIDING ADEQUATE PERSONNEL WITH THE BEST POSSIBLE TRAINING AND QUALIFICATIONS FOR SUCH SERVICES"

Leading out of the studies mentioned under (d) the Commission will doubtless consider the problem of attracting to the health professions adequate numbers of academically qualified and well-motivated recruits. The economic, social and other reasons for the current decline in well-prepared applicants for training should be explored.

The role of The Canadian Medical Association in approving hospitals for the training of junior interns and that of the Royal College of Physicians and Surgeons of Canada in identifying hospitals for advanced graduate training in the specialties are pertinent. The approved training programs for laboratory technologists, radiological technicians, physical and occupational therapists, university and hospital training schools for nurses, training facilities for nurses' aides and other health workers should be assessed.

The Association of Canadian Medical Colleges will present a definitive submission on undergraduate medical education and the pressing problems associated with this fundamentally important element of training.

The particular responsibilities of the teaching hospitals should be studied.

Continuing education of the practising physician by refresher courses, institutes, symposia and conventions should be examined as well as the profession's efforts to bring to the doctor in his own locality postgraduate education in the form of clinics and scientific meetings.

The financial problem of the unestablished practitioner may be looked at as well as the desirability of achieving optimum distribution. The effect of income tax regulations on expenses of practice and of refresher courses have some pertinence in this connection.

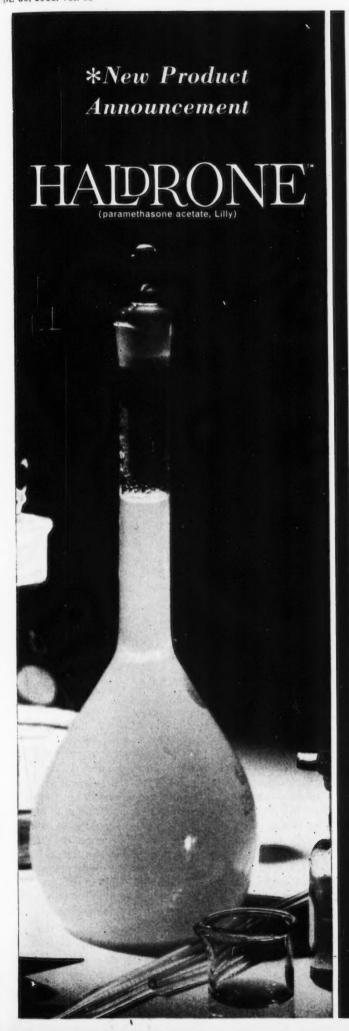
### (f) "The Present Physical Facilities and the Future Requirements for the Provision of Adequate Health Services"

Existing deficiencies in facilities should be studied here, together with the cost of correcting them. These deficiencies will consist of hospital beds of all types, rehabilitative facilities, teaching and research diagnostic facilities as well as the observed deficiencies in public health and sanitary arrangements.

### (g) "The Estimated Cost of Health Services Now Being Rendered to Canadians with Projected Costs of Any Changes that May be Recommended for the Extension of Existing Programs or for Any New Programs Suggested"

Previous attempts to estimate the cost of health services have been prepared on a national basis to include governmental and private expenditures. It is assumed that the Commission will provide itself with this basic information and that it will be made available to interested parties for their calculations on future requirements.

The projected costs of correcting deficiencies will will arise out of each submission's appraisal of existing and projected requirements. The cost estimates will necessarily be inexact but they are unlikely to err on the side of over-estimation.





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Haldrone, 2 mg., is approximately equivalent to

Cortisone										25	mg.
Hydrocortisone .										20	mg.
Prednisone or pre	edi	nis	olo	ne						5	mg.
Triamcinolone or	n	iet	hy	lp	rec	lni	iso	lor	ne	4	mg.
Dexamethasone.										0.75	mø.

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Eli Lilly and Company (Canada) Limited Toronto, Ontario (Continued from page 810)

(h) "The Methods of Financing Health Care Services as Presently Sponsored by Management, Labour, Professional Associations, Insurance Companies, or Any Other Manner"

Information as to the specific insurance arrangements listed should be available from a variety of sources. The difference between service and indemnity programs and the attitude towards co-insurance should be explored.

The medical profession's submission will elaborate on the Statement on Medical Services Insurance, and an outline of the development of prepaid medical care under the sponsorship of the profession will be provided. Trans-Canada Medical Plans' national submission would be particularly appropriate here.

(i) "The Methods of Financing Any New or Extended Programs which may be Recommended"

The possibility of personal financing of new or extended programs by the self-supporting elements of society should be explored in the first instance.

In the case of persons in need of assistance by reason of inadequate income, age or state of health, it appears likely that public funds will be required. The coverage of the currently uninsurable groups by subsidy of premium or otherwise would in our view be desirable. The realities of a means or needs test should be examined. The taxing powers of Federal and provincial governments bear a direct relationship to their ability to finance new or extended programs and the Commission will doubtless examine very carefully the economics of the situation in relation to traditional Dominion-provincial spheres of authority in matters of health.

(j) "The Relationship of Existing and Any Recommended Health Care Programs with Medical Research and the Means of Encouraging a High Rate of Scientific Development in the Field of Medicine in Canada"

The Association of Canadian Medical Colleges and the Medical Research Council will likely take the lead in discussing research. C.M.A. policy states that insurance mechanisms should not act to inhibit research, and it is inferred that research, whether fundamental or clinical, should not be basically dependent on finances derived from medical or hospital services insurance.

(k) "The Feasibility and Desirability of Priorities in the Development of Health Care Services"

This will vary with each presentation as different needs will require different priorities. We should, however, keep in the foreground the need for subsidized medical insurance for specified groups, the requirements of medical education and the need to further develop many services, notably mental health services, which have traditionally been the responsibility of governments. The estimate of costs previously ascertained will doubtless influence the Commission in assigning priorities.

(1) "Such Other Matters as the Commissioners Deem Appropriate for the Improvement of Health Services to all Canadians"

This is a catch-all category for the presentation of any matter which does not seem to fit in any preceding category.

## BOOK REVIEWS

CANCER-THE SIGNIFICANCE OF DELAY. Robert Sutherland. 206 pp. Butterworth & Co. (Publishers) Ltd., London; Butterworth & Co. (Canada) Ltd., Toronto, 1960. \$6.00.

The reader who only seeks to discover the effect of delay on the results of treatment of cancer will find to his surprise that the discussion of this subject is confined to the final chapter of this treatise. Much of the author's efforts have been devoted to a review of the difficulties of defining cancer, of assessing the degree of its malignancy and the extent of dissemination, and a survey of current opinion concerning the influences of the tumour cell, its host and its environment on the course of the disease.

From this basis the author examines the evidence for the claim that early treatment improves prognosis. A comparison of five-year survival rates of treated and untreated cancer of various sites with those for patients who underwent radical treatment at an early stage supports this thesis. But the figures provide no

cause for complacency. In the first place, it is pointed out that five-year survival rates are an inadequate expression of cure and, in the second place, the differences in rates are not great. Furthermore, in some series (e.g. cancer of the breast) it would appear that the average survival is greater in those who have delayed the longest before receiving treatment. This has led some students of the disease to come to the conclusion that the biological type of cancer is the major factor in determining the outcome for the individual. The author has reviewed the literature describing the effect of delay on operability and "radiocurability", on the size of the tumour, on the progression of the tumour towards greater malignancy and on metastasis.

After examining the evidence, he concludes that "although by the time they are noticed many cancers are already fatally progressed in malignancy, others are not; since earlier treatment may mean life instead of

(Continued on page 814)

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(Continued from page 812)

death for some, we must do everything we can toensure that it is given to all."

These are subjects of much debate and, in pursuit of objectivity, Dr. Sutherland has presented the evidence in considerable detail. Indeed, it may be suggested that had some tables been deleted and some of the discussion been abbreviated the presentation would have been made more readable without sacrifice of its purpose.

Nevertheless, Dr. Sutherland is to be congratulated for having produced a most useful survey of this controversial field and having drawn attention anew to the fact that those who treat cancer must "divide the honours of success and the dismay of failure with Nature's efforts".

EINFACHHEIT UND SICHERHEIT BEI MAGEN UND DARMOPERATIONEN. Heinrich Westhues. 75 pp. Illust, Georg Thieme Verlag, Stuttgart, West Germany; Intercontinental Medical Book Corporation, New York, 1961. \$7.25.

In this small and beautifully illustrated volume the author presents his 35 years' experience in gastric, colonic and rectal surgery. He is a proponent of the aseptic anastomosis which in his experience is simpler, faster and safer than the open one, provided that a special coagulating and protective forceps is used. The coagulation is carried out by heating the instrument in boiling water. This, according to the bacteriological and histological research of the author, results in the destruction of all the pathogenic micro-organisms and thus in an aseptic well-healing anastomosis.

The procedure and its advantages are well documented. Although the necessary instruments are not yet available in this country, the book is recommended to the attention of surgeons.

ASSESSMENT OF THE ACTIVITY OF DISEASE. J. S. Lawrence. 252 pp. Illust. H. K. Lewis & Co. Ltd., London, 1961. £2 2s. net.

"Though several books dealing with the erythrocyte sedimentation rate and similar non-specific tests of disease activity have appeared during the last 40 years, no very comprehensive work has, to the author's knowledge, been written in the English language." Dr. Lawrence's introduction to his book denotes the particular value of this volume.

In this work the world literature is summarized and leavened by the author's personal investigations. The first part of the volume describes in detail various parameters of disease activity. These include changes in leukocytes, plasma proteins, the erythrocyte sedimentation rate and plasma viscosity. Various factors modifying the results of these tests are documented. This portion of the book should provide an area of unusual interest for one who desires to acquire an intimate knowledge of these tests.

The remainder of the work is a consideration of a great variety of diseases, and the changes which may be expected in the non-specific indices are noted. Some of the data appear trivial and of doubtful applicability to ordinary clinical medicine.

This work is recommended for its extensive bibliography and should be in medical libraries. PSYCHOSOMATIC ASPECTS OF PAEDIATRICS. Study Group of the Society for Psychosomatic Research held at the Royal College of Physicians, May 1959. Edited by Ronald MacKeith and Joseph Sandler. 155 pp. Pergamon Press Ltd., Oxford; Pergamon Press, Inc., New York, 1961. 50s. net.

This book contains the papers and discussions of two Symposia of a Study Group of the Society for Psychosomatic Research held under the auspices of The Royal College of Physicians and Surgeons of England. The meetings, held primarily for pediatricians, include papers on symptomatic disorders having psychological and physiological components, such as chronic constipation, encopresis and recurrent pains. The papers reflect the basic orientation of the authors, the pediatricians emphasizing the physiological and structural defects of the conditions: and the psychiatrists, the dynamic and psychosocial aspects.

There are good papers on identification, psychological development, and learning theory as it applies to personality development. Bowlby presents a comparatively new viewpoint as he describes personality development from the standpoint of ethology. He suggests that man has an inborn matrix of perceptual and expressional patterns that serve to distinguish him from other species and proposes that the field be studied more extensively. He suggests, for instance, that the infant smile is a species-specific pattern solicited by the perception of the human face, usually the mother. He departs from the position of the learning theorists who postulate perception and behaviour as learned rather than inborn patterns.

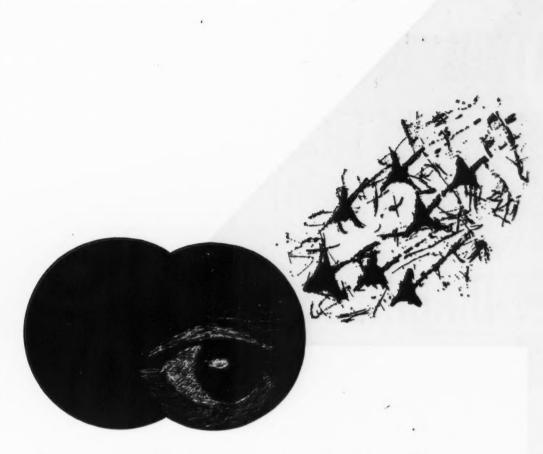
There are papers devoted to psychosomatic theory and research. They again reflect the backgrounds and views of men from different specialties and disciplines. The book may be properly described as a collection of papers and discussions on a few selected topics. The individual papers are interesting and some are quite good. The book may be helpful to those interested in the subject of communication between pediatrician and child psychiatrist.

ARTIFICIAL FEEDING IN INFANCY. Pediatric Series. Andrew Bogdan. 24 pp. Tutorial System Publications, England; McAinsh and Company Limited, Toronto, 1961.

The aim of this 25-page paper-back book is to set forth concisely the general principles involved in the artificial feeding of healthy infants. The reviewer feels that this aim is accomplished in a very readable and satisfactory fashion, and that the book could be useful to nurses, house officers and practitioners.

The general principles of technique, sterility, volume requirements and caloric requirements are applicable in any geographic setting. On the other hand, the specific details are not applicable beyond the British Isles. The author makes no mention of the preparation of a full day's feeding and refrigeration until needed, which is the usual procedure in North America. He makes no mention of terminal sterilization, a technique which is simple and quite popular on this continent. He refers to the "Milton method" of cleansing bottles, a technique which is unknown to the reviewer and his confrères (all pediatricians).

In summary, the book outlines accepted principles satisfactorily, but details of formula preparation are such that the book will be of doubtful value to Canadian doctors.



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Lehmann, H. E.: Canad. Psychiat. A. J.

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# antidepressant / antianxiety agent for mixed depression and anxiety

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PARNATE\*, 10 mg., as the sulfate (brand of tranylcypromine) a new monoamine oxidase inhibitor

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Supply: 'Parstelin' Tablets, in bottles of 50 and 250. Also available: 'Parnate' Tablets, 10 mg., in bottles of 50. 'Stelazine' Tablets, 1 mg. and 2 mg., in bottles of 50 and 500.



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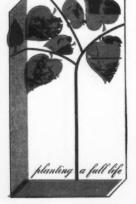
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Please tear off and mail this coupon





Please send me:	☐ Meal Planning Chart	
address		M.I
audito		

## MEDICAL NEWS in Brief

(Continued from page 801)

### ANNUAL MEETING OF ASSOCIATION OF AMERICAN MEDICAL COLLEGES

The 1961 Annual Meeting of the Association of American Medical Colleges will be held November 13-14 at the Queen Elizabet Hotel, Montreal.

A preliminary program for thes two days includes the following.

November 13-

For the morning:

Statement of Welcome, Presiden Association of Canadian Medica Colleges; "Goal of the Federal Government in Medical Education, speaker pending; "An Inquiry into Medical Teaching", George E. Miller, M.D.; "Seminars on Medical Teaching: A Recapitulation", Edwin F. Rosinski, Ed. D.; Panel discussion. "Floribility in the Time cussion, "Flexibility in the Time for Preparation of the Physician", John A. D. Cooper, M.D., Robert H. Alway, M.D. and Samuel P. Asper, Jr., M.D.

For the afternoon:

"A Four-Year Integrated Curriculum in Radiobiology", William H. Elliott, Ph.D.; "Developments in High School Biology and Their Implications for Medical Education", Lester J. Evans, M.D. and Arnold Grobman, Ph.D.; "Medical Education at Western Page 11. Education at Western Reserve University: A Progress Report", T. Hale Ham, M.D.; Panel discussion, "Problems of Admission and Liaison Pertaining to Medical Colleges, Secondary Schools, and Undergraduate Institutions", Clifton W. Emery, Ph.D., Daniel H. Funkenstein, M.D. and Mr. Calvert W. Bowman.

For the evening:

Annual Banquet of the Association, with Presentation of the Borden Award in the Medical Sciences for 1961, by S. Marsh Tenney, M.D., Chairman, Com-mittee on the Borden Award Dean, Dartmouth Medical School Presentation of the Abraham Flexner Award for Outstanding Service to Medical Education, by Joseph C. Hinsey, Ph.D., Director New York Hospital - Cornell Medical Center; and the Fourth Alan Gregg Memorial Lecture, "The Epic of Alan Gregg", by Wilder G. Penfield, M.D.

(Continued on page 24)

NEW comprehensive

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with the
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potent
enzyme
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-also unsurpassed potency for digestion of starch, protein and cellulose

- -the only digestant with Lipancreatin,\* proven superior to Pancreatin N.F.
- -the only digestant with fat-splitting lipase activity 12 times as great as that of Pancreatin N.F.

When the question is digestion because of your patient's inability to handle fat, starch, protein or cellulose, you can provide dependable relief with COTAZYM-B, which contains the essential pancreatic enzymes lipase, trypsin and amylase, plus bile salts and cellulase. A daily dose of 6 COTAZYM-B tablets is sufficient to emulsify and digest 50 Gm. of dietary fat, and to digest all of the protein and starch in a typical diet (100 Gm. protein, 250 Gm. starch) and 480 mg. cellulose.

Dosage: 1 or 2 tablets with water just before each meal.

Supply: Bottles of 48 tablets.

Write for samples and comprehensive literature.

NEW

Lipancreatin Bile Salts Cellulase

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\*The Significance of Lipancreatin (Pancreatic Enzymes Concentrated 'Organon')

A product of original Organon research, lipancreatin provides for the first time in digestant preparations a known, constant amount of fat-digesting lipase in addition to trypsin and amylase. It surpasses in assayable digestive activity all presently available pancreatin preparations.

### MEDICAL NEWS in brief (Continued from page 18)

### November 14-

"Medical Education in Latin America Today", Abraham Horwitz, M.D.; "The World Role of the Association of American Medical Colleges", H. van Zile Hyde, M.D.; "Educational Costs in Teaching Hospitals", Howard Bost, Ph.D. and Mr. Augustus J. Carroll; "Hospital Community Planning, Teaching Hospitals, and Medical Schools", Karl S. Klicka, M.D.; "The Revised Part III Examination of the National Board and its Results", John P. Hubbard, M.D.

### PREMALIGNANT CONDITIONS OF THE VULVA

Except for the repeated applications of carcinogens such as mineral oils, and possibly for chronic granulomatous venereal disease, a local cause for the squamous cell cancer of the vulva is not known. Like skin cancer in general, involutional changes associated with ageing are probably important predisposing factors.

Invasive cancer often begins by way of a field change which may be widespread and in which disorderly epithelial activity is the characteristic histological change. This activity is sometimes so pronounced as to justify the term "cancer in situ", but in lesser degrees should not be labelled "leukoplakia", for it bears no constant relationship to hyperkeratinization, which is implicit in this name.

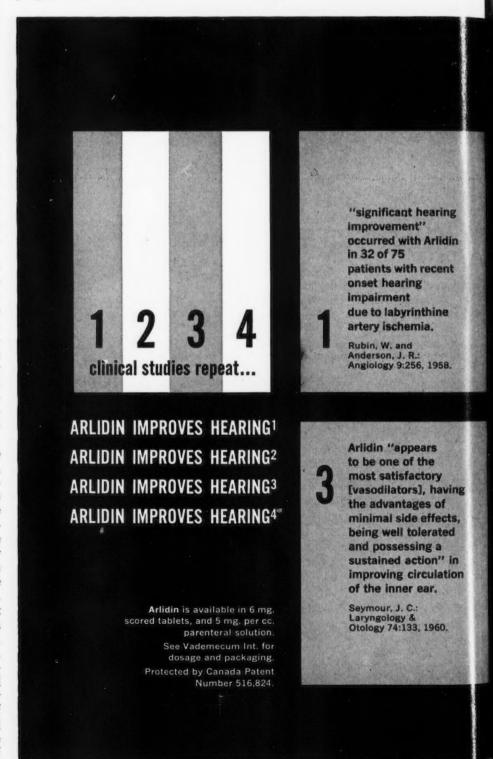
There is as yet no evidence to justify the view that leukoplakia, leukoplakic vulvitis, kraurosis (primary atrophy), and lichen sclerosus vel atrophicus are separate disease entities. Judged by either macroscopic or microscopic criteria, these represent no more than a variety of skin reactions to adverse factors which, although obscure, are more likely to be "general" than "local". The type of reaction is dependent on the environment of the vulva and not on the underlying cause. Jeffcoate and Woodcock (Brit. M. J., 2: 127, 1961) therefore suggest that all these names should be abandoned, since they hinder rather than help the elucidation of their causes. In their place, and pending further knowledge, the non-committal inclusive term of

chronic epithelial dystrophy is proposed as one convenient for clinic-

al practice.

Clinically,—earcinoma in situ can simulate a chronic epithelial dystrophy, and can be excluded only by biopsy. Histological examination of all dystrophies reveals abnormal and disorderly epithelial activity in only 4% to 8% of cases. When it does, there is probably a 10% chance of the subsequent development of cancer, but vulvectomy is nevertheless justified as a prophylactic measure.

In the remaining majority of cases of chronic epithelial dystrophy, there is no special risk of malignant change and vulvectomy is not justified as a cancer preventive; and as an empirical treatment, it does not give satisfactory results even when the skin change appears to be strictly limited and demarcated. Unless the cause is determined and eradicated, epithelial dystrophy recursin approximately 50% of case treated by partial or total vulvectomy.



# PRESIDENT KENNEDY'S YOUTH FITNESS PROGRAM

Details of President Kennedy's Youth Fitness Program have been outlined by the American Medical Association in a news release on August 25, 1961.

The program consists of five ecommendations:

"That the preschool physical appraisal of children be broadened include screening tests for strength, agility and flexibility. These tests can be given in less

than a minute, and in a very small space.

"Pupils who fail the tests for strength, agility, and flexibility be required to participate in progressive developmental exercises and activities designed to build up muscular structures and enable underdeveloped students to meet minimal fitness levels.

"The screening tests be repeated every six weeks until all students reach minimum levels. Students with health limitations which preclude vigorous participation would be put on a program consistent with their physical condition. All medical and health needs should be attended to, of course.

"All students spend a minimum of 15 minutes per day participating in sustained conditioning exercises and developmental activities designed to build vigour, strength, flexibility, endurance, and balance. This, of course, is part of a broader physical education program.

"Students be given a comprehensive test at the beginning and end of the semester. The first test would establish their present status and perhaps motivate them to improve their physical condition. Parents would have a clear understanding of where their child stands in the physical fitness scale. The second test would measure the child's progress made during the semester."

The American Medical Association pointed out that it is important for each school undertaking Wilkinson's fitness program to make certain that the program is carried out under the supervision of a physician. Careful preliminary physical examinations, to make certain that there are no contraindications to physical training, are urged for each student. A child's basic physical fitness is tested in the following manner:

"Strength is tested by the pull-up for boys; the modified pull-up for girls. Find something to use for a chinning bar. Boys grasp the bar with palms forward. Hang with arms and legs fully extended and feet free of the floor. The boy pulls himself up until his chin is over the bar. Then lowers himself slowly until the arms are fully extended. Then up again. Any boy should be able to do one pull-up. If he's 14, the minimum is two; if he's 16 the minimum is three.

"For girls, adjust the bar to chest level. Girls extend their legs under the bar so their arms hang, fully extended, straight down from the bar. The girl pulls herself up until chest touches the bar, then lowers herself until the arms are fully extended. Then up again. Girls should be able to do a minimum of eight modified pull-ups.

"Flexibility (and abdominal strength) is tested by the sit-up for boys and girls. The child lies on his back, legs extended and feet about 12 inches apart. The hands

vascular insufficiency of the labyrinth is an important etiologic factor in sudden perceptive deafness... "vasodilators [Arlidin] are of considerable value."

Wilmot, T. J. and Seymour, J. C.: Lancet 1:098, 1960.

early cases of sudden perceptive deafness should be treated by immediate stellate block "supplemented by the most effective vasodilator drug [Arlidin] ... energetic measures to retain blood supply to the inner ear are imperative."

Wilmot, T. J.: J. Laryngology & Otology 73:466, 1959.

# impaired hearing tinnitus vertigo

when due to ischemia of the inner ear...

arlidin

brand of nylidrin hydrochloride N.N.D.

Clinical benefit in approximately 50% of cases of recent onset hearing loss treated with adequate vasodilator and other supportive therapy is also reported by Sheehy.

Sheehy, J. L.: Laryngoscope 70:885, 1960.

NOTE — before prescribing Arlidin the physician should be thoroughly familiar with general directions for its use, indications, dosage, possible side effects and contraindications, etc. Write for complete detailed literature.

arlington-funk laboratories, division

u. s. vitamin corporation of canada, ltd.

1452 Drummond Street, Montreal, Canada

(Continued on page 26)

MEDICAL NEWS in brief

(Continued from page 25)

are on the back of the neck with fingers interlaced.

"Hold his ankles, keeping the heels on the floor. Now he sits up, twisting the trunk and touching the right elbow to the left knee. Then he goes back down and up again, this time touching the left elbow to the right knee. Boys should do at least 14 of these, girls at least 10, in rapid succession.

at least 10, in rapid succession.

"Agility is tested by the 'squat thrust' for boys and girls. Start at

the position of attention. Action is carried out in four movements.

"First, bend the knees and place hands on the floor in front of the feet. Arms may be between, outside of, or in front of bent knees.

"In one movement, thrust the leg backward so the body is straight from shoulders to heels (the normal push-up position). Now, in one movement, return to the squat position, and in the final movement return to erect position.

"Time this test. Boys should do a minimum of four correct squat thrusts in 10 seconds, girls three. Make sure the child returns to a fully erect position at the end of each squat thrust.

"If your children passed these tests, they probably could pass a more elaborate physical achievement test."

### UN COURS DE MEDECINE ET HYGIENE NUCLEAIRES A L'UNIVERSITE DE MONTREAL

L'Université de Montréal organise un cours de Médecine Biologie et Hygiène Nucléaires, dans le cadre de l'Extension de l'Enseignement et sous les auspices de l'Ecole d'Hygiène. Ce cours s'adresse aux médecins et aux biologistes inté ressés aux applications de l'énergie nucléaire et des radiations en médecine et en santé publique. Le cours est divisé en deux parties, chacune pouvant être suivie séparément, au cours de la même année cu en deux années différentes. Les conférences sont données en français, mais un cours semblable pourrait être considéré en anglais, si le nombre d'étudiants de langue anglaise est suffisant.

Les sujets traités dans les deux parties du cours sont les suivants: lère partie (Cours N° 44), Notions fondamentales de Médecine et d'Hygiène Nucléaires. Professeur: Dr Joseph Sternberg.

Notions fondamentales de physique et de chimie nucléaires appliquées à la Médecine et à la Biologie. Théorie et applications des instruments basiques de mesure de la radioactivité; organisation du laboratoire des radioisotopes et de radiation. Normes de protection contre la radiation, notions de "Health Physics".

Revue des applications des radioisotopes et de la radiation en Médecine et en Biologie: biochimie, physiologie, pharmacologie, toxicologie, nutrition, endocrinologie, etc. Action de la radiation sur la matière: maladie de la radiation; radiation et cancer, génétique et radiations. Radiation et Santé Publique: contamination du milieu environnant par les substances radioactives, déchets radioactifs. Applications de l'énergie nucléaire en temps de paix; la guerre atomique, rôle du médecin et de l'hygiéniste.

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IN MINUTES...FOR HOURS...
ORALLY

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**INHERENT SUSTAINED ACTION**—After absorption theophylline is slowly eliminated during a 9-hour period. Clinically *proved* relief and protection day and night with t.i.d. dosage. 1,3-6,8,9

NO UNNEÉDED SIDE EFFECTS—Since Elixophyllin does not need "auxiliaries," it contains no ephedrine—no barbiturate—no iodide—no steroid. Gastric distress is rarely encountered.<sup>8,9</sup>

Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydroalcoholic vehicle (alcohol 20%).

### ACUTE ATTACKS:

single dose of 75 cc. for adults, 0.5 cc. per lb. of body weight for children.

### 24 HOUR CONTROL:

for adults 45 cc. doses before breakfast, at 3 P.M., and before retiring, after two days, 30 cc. doses. Children, first 6 doses 0.3 cc.—then 0.2 cc. per lb. of body weight as above. Average increase in rital transcits produced by Elegiphylus 75 oc., in acute astimatic attacks. 3

300 cc. 565 cc. 807 cc. 39%

MINUTES

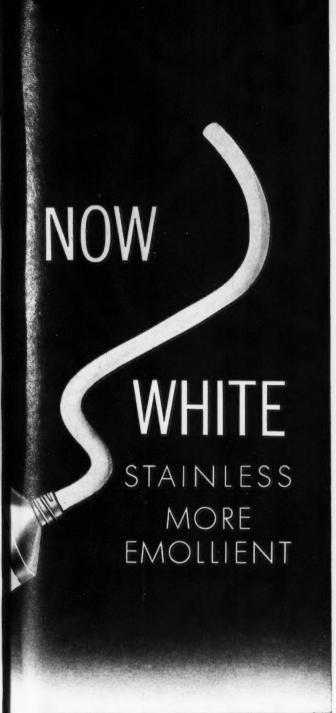
5 15 30

REFERENCES: 1. Kessler, F.: Connecticut M.J. 21:205 (March) 1957. 2. Schluger, J.; McGinn, J.T., and Hennessy, D.J.: Am J. Med. Sci. 233:296 (March) 1957. 3. Kessler, F.: Med. Times (Oct.) 1959. 4. Burbank, B.; Schluger, J., and McGinn, J. Am. J. Med. Sci. 234:28 (Lily) 1957. 6. Spelleman, A.D.: Ann. Allergy 15:270 (June) 1957. 6. Greenbaum, J.: Ann. Allergy (May-June) 1958. 7. Waxler, S.H., and Shack, J.A.: J.A.M.A. 143:735 (1950). 8. Bickerman, H.A., and Barach, A.L., in Modell W.: Drugs of Choice 1960-1961, S.L. Louis, The C.V. Mosby Company, 1960, p. 516. 9. Wilhelm, R.E., Conn, H.F.: in Current Therapy—1961, Philadelphia, W.B. Saunders Company, p. 417.

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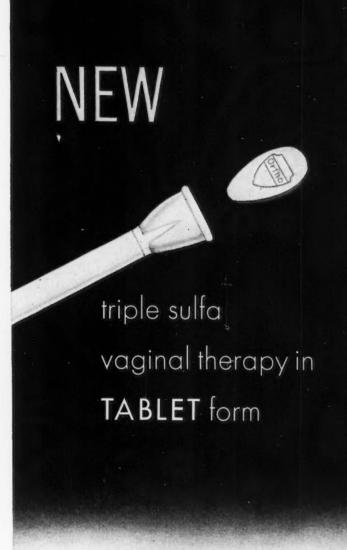


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MEDICAL NEWS in brief (Continued from page 26)

Nombre de cours: 35 (75 heures, dont 16 démonstrations ou travaux pratiques au cours du 2ème semestre). Les cours seront donnés mardi soir entre 7.30 et 9.30 débutant le 3 octobre. Frais de scolarité: \$75.00.

2ème partie (Cours N° 45), Applications médicales des Radioisotopes et de la Radiation. Professeurs: Dr Joseph Sternberg et conférenciers invités.

Application des radioisotopes au diagnostic clinique: le radioiode et le diagnostic des affections thyroïdiennes; les radioisotopes dans les maladies du sang et de la circulation; procédés de médecine nucléaire en gastro-entérologie, chirurgie, neuro-chirurgie, cancérologie, orthopédie, microbiologie et immunologie, recherche clinique, pédiatrie, médecine interne, etc.

Thérapie par les substances radioactives: théorie et applications.

Hygiène Nucléaire: études épidémiologiques, génie sanitaire, etc. faites avec des substances marquées. Stérilisation des aliments et des médicaments par la radiation.

Des conférences spéciales seront faites suivant l'orientation des étudiants; des visites pourront être organisées aux laboratoires et institutions appliquant des techniques de médicine et de biologie nucléaires.

Les médecins intéressés pourront obtenir une attestation nécessaire pour la demande de l'autorisation gouvernementale en vue de l'utilisation des radioisotopes en clinique.

Nombre de cours: 25 (50 heures, dont 25 heures de travaux pratiques ou de démonstrations cliniques). Les cours théoriques seront faits jeudi soir de 7.30 à 9.30; les travaux pratiques ou cliniques seront faits à des endroits et dates fixées ultérieurement. Frais de scolarité: \$60.00.

Pour obtenir des informations supplémentaires, s'adresser à l'Extension de l'Enseignement, Université de Montréal, C.P.6128 (Tél. RE. 3.99.51, local 246), ou directement au Dr Joseph Sternberg, Institut de Microbiologie et d'Hygiène, C.P. 6128, Tél. RE 3.53.94.



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# ANNOUNCEMENT OF HEMATOLOGY COURSE

University of California Continuing Education in Medicine will present a three-day course in "New Concepts in Hematology", beginning November 29 at the U.C. Medical Center. The program will bring together scientists in the fields of biochemistry, physics and allied sciences who are contributing to major changes in hematology. Both the mechanism of disease and modern treatment will be stressed.

Program chairmen are Hugh Fudenberg, M.D., Hematology Research Laboratory, U.C. School of Medicine, and Ralph O. Wallerstein, M.D., Hematology Research Laboratory, San Francisco General Hospital and University of California Hospital.

Further information and registration forms may be obtained from Continuing Education in Medicine, University of California Medical Center, San Francisco 22, Calif., U.S.A.